

**SOME ASPECTS OF LEPTOSPIROSIS
IN
THE JUNGLES OF EASTERN AND WESTERN MALAYSIA:
A HAZARD OF MILITARY SIGNIFICANCE.**

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PLATE 1.

Standard ECG leads of case 1.

3rd day of disease showing ventricular extrasystoles, tachycardia and low T waves in I and II, inverted T wave in III with a low voltage tracing.

PLATE 2.

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PLATE 3.

Daily chart showing characteristic response to early and adequate penicillin therapy.

PLATE 4.

2-hourly chart showing characteristic response to early and adequate penicillin therapy. Note the effect on the temperature, pulse rate and blood pressure.

SIGNED DECLARATION.

This is to certify that I, John Mackay-Dick, have written all of this thesis on 'Some Aspects of Leptospirosis in the Jungles of Eastern and Western Malaysia: A Hazard of Military Significance'.

I wrote the entire paper by Mackay-Dick and Watts (1949) when I was Lieutenant-Colonel, Officer in Charge of Medical Division, 94 (Hamburg) British Military Hospital, British Army of the Rhine but the work was part of a group as already indicated.

In addition to writing the entire paper by Mackay-Dick and Robinson (1957) on 'Penicillin in the Treatment of 84 Cases of Leptospirosis in Malaya' I planned and directed this work until 140 laboratory proved cases of leptospirosis had been treated under my direction. (Mackay-Dick and Robinson 1959a; Mackay-Dick and Robinson 1959b): in Malaya (1955-58) I was Officer-in-Charge, Medical Division of British Military Hospital, Kinrara, Kuala Lumpur, and later Commanding Officer, when this work was carried out.

My additional observations on leptospirosis, its early diagnosis, treatment, epidemiological factors, preventive measures and its significance as a hazard of military significance were crystallised in Eastern Malaysia (Sabah and Sarawak) when I was the Assistant Director of Medical Services (the Senior Medical Appointment) Headquarters, Land Forces Borneo, and in Brunei, during the last year of the Indonesian Confrontation with Greater Malaysia (1966).

Where appropriate I have made acknowledgment to published works of others. In addition I have made acknowledgment to personal

communications from:

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* R.M.O. = Regimental Medical Officer.

+ Bn. = Battalion.

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M.B., B.Sc., F.R.C.P., Director-General Army Medical Services, to
form part of my address to the Edinburgh Branch of the Royal Society
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Course on Occupational Health in Agriculture, held at the University
of Dundee on 16th October, 1968.

Thanks are also due to the Central Office of Information for
the photographs taken in Malaysia during the Indonesian Confrontation;
these photographs are Crown copyright.

Because the binomial nomenclature ('*L. batavia*' etc.) for leptospirae is no longer valid, and to avoid needless repetition, the word 'serotype' where it is implied has been omitted from this thesis.

JOHN MACKAY-DICK.

SUMMARY.

In the jungles of Malaysia there is a large natural reservoir of leptospirosis, a disease of significance as a military hazard particularly when 'mass' infections may necessitate the withdrawal of a patrol from operations. Portals of entry are the skin, conjunctiva, nasal and buccal mucosa, anus and genitals. Conditions of special exposure, when chemoprophylaxis or abortive treatment may be considered, and preventive measures, are described as well as the infectious environment with special reference to water as a vector, and where and when it may be considered safe to bathe. The case incidence is proportional to the amount of time spent on jungle operations; which may explain the variation in the incidence of leptospirosis in British security forces in operations in Malaysia (1948-61) and in United States Army personnel in Vietnam. Subclinical cases occur; but normally in at least 85 per cent of cases leptospirosis is a benign self limited febrile disease (3-15 days) with inconstant secondary fever of indeterminate origin, varying duration and associated with recrudescence of symptoms. An occasional death occurs. Probably over 90 per cent of cases are anicteric. Significant lower nephron nephrosis occurs in around 6 per cent of cases; and haemorrhagic phenomena are present in less than 20 per cent. Fulminating haemorrhagic pneumonia is rare. Multiple and repeated infections occur. Generally any febrile illness in patients from leptospiral environments characterised by headache, myalgia, conjunctival suffusion and

gastrointestinal symptoms, in the presence of urinary abnormalities, warrants the diagnosis of leptospirosis unless proven otherwise; but the urine may be normal or may just show a trace of albumin. The key to successful treatment is early diagnosis and adequate chemotherapy, using crystalline penicillin parenterally in the predominantly septicaemic phase of the illness together with the maintenance of water and electrolyte balance and otherwise masterly inactivity in the normal case; no matter when adequate penicillin is given in the illness there is no secondary fever, no residual impairment of renal function and no late complications such as iritis, etc. Renal dialysis is life saving in severe lower nephron nephrosis. Vaso-constrictors are to be avoided in the treatment of hypotension as they may be lethal. Prednisone may be of value in complicated cases and as a 'cover' for penicillin, in cases treated early, when there occurs a characteristic Herxheimer-like reaction.

Laboratory diagnosis is normally by blood culture and serological tests; but with early and adequate penicillin therapy peak serological titres may be so low, and in some cases serum antibodies may not be detectable in the ensuing weeks, that the only means of a diagnosis may be positive blood culture: yet the latter may be negative when blood samples are taken after penicillin has been given or because of contaminants, and in such circumstances the Herxheimer-like reaction may be of special diagnostic significance.

A knowledge, by commanders at all levels on active service in the jungles of Eastern and Western Malaysia of reservoir hosts of infection, of leptospiral environments, of sources and routes of

infection, of preventive measures and evasive action regarding leptospirosis, as well as the extremes of the incubation period (4-21 days) are of significant importance particularly when the effectiveness of a jungle patrol may be neutralised to such an extent that it has to be withdrawn from an important operation and so jeopardise its success.

INTRODUCTION.

My interest in leptospirosis was aroused in Germany where the protean manifestations of canicola fever, including iritis presenting in one case some 78 days from the onset of the illness, suggested to me that this benign disease - benign not because of the severity of the symptoms but because of its insignificant mortality rate - must, almost inevitably, be frequently misdiagnosed and masquerade under diverse diagnoses (Mackay-Dick and Watts 1949). Subsequently from what I heard about the increasing frequency with which leptospirosis was being diagnosed amongst security forces in Malaya (1950-54) and the divergent opinions regarding the value of penicillin I determined to make a special study of leptospirosis with special reference to its epidemiology and prevention, clinical manifestations, early diagnosis and the results of treatment with parenteral crystalline penicillin when given early enough, often enough and in large enough doses.

I prepared my plan of management of these cases prior to my arrival in British Military Hospital, Kinrara, Kuala Lumpur, Malaya (now Western Malaysia) in May, 1955 as Officer-in-Charge, Medical Division. The intention was that in every case of pyrexia of uncertain origin (PUO) admitted to hospital, a detailed history and clinical examination, in addition to all appropriate laboratory procedures, together with the institution of a regimen of parenteral crystalline penicillin would all have taken place within 24 hours

of admission to hospital; but we did not always succeed in keeping to this schedule. The penicillin regimen was 3.6 mega units in the first 24 hours, i.e. 600,000 units of crystalline penicillin intramuscularly stat and repeated four hourly to complete 24 hours: then 2.4 mega units daily thereafter in six hourly dosages of 600,000 units to complete seven days chemotherapy in all.

Much emphasis was laid on the accurate assessment of the day of the illness on which penicillin was begun because, initially, leptospirosis is a septicaemia and that is the phase of the illness when a leptospiraecidal drug, such as penicillin, may be expected to provide significant evidence of therapeutic response and clinical improvement. Too often the day of illness has been regarded as being synonymous with the day of admission to hospital. Hence the main reason, in my opinion, why penicillin has been so often regarded as being of no therapeutic value in leptospirosis; another suggested reason is inadequate dosage of penicillin.

I was unable to begin my work until November, 1955 as a trial using tetracyclines was being carried out in military hospitals in Malaya under the direction of the Consulting Physician, Far East Land Forces (FAELF).

I then selected a newly arrived young National Service medical officer (J.F. Robinson) to act as my assistant. I briefed him on leptospirosis and on my plan of action. All cases of pyrexia of uncertain origin (PUO) in security forces admitted to British Military Hospital, Kinrara were to be seen by us and appropriate action taken as indicated above, and a special ward was set aside

for suspected cases of leptospirosis.

We published a paper on 'Penicillin in the treatment of 84 cases of leptospirosis in Malaya' (J.Roy.Army.Med.Cps. (1957), 103, 186). This was accepted as providing significant evidence of the value of penicillin in leptospirosis (Leading Article (1958) Brit. Med.J., i, 58), which has been confirmed among others by Turner, (1967; 1969), Gsell (1966) and by Cook (1959). Quote - 'The pattern of response described by Mackay-Dick and Robinson is uniform, and sufficiently reliable to be used as a diagnostic test over the first 24 hours. The severity of the 'penicillin-leptospiral reaction' occasionally causes anxiety and the management of this remains a matter of opinion The regime described by Mackay-Dick and Robinson, with slight modifications has now become the standard treatment for leptospirosis in military hospitals in Malaya. Penicillin is found to be consistently and speedily effective regardless of the leptospiral strains involved.' (Cook, 1959).

In all before I left Malaysia in March, 1958, 140 laboratory proved cases of leptospirosis had been treated on my penicillin regimen. There were no deaths, no cases of secondary fever and no late complications. The pattern of response to treatment was as outlined by Mackay-Dick and Robinson (1957) and has been repeatedly confirmed by my colleagues in Malaysia and Singapore ever since. Penicillin was also used in the treatment of leptospirosis in Commonwealth forces in Sabah and Sarawak (Eastern Malaysia), and in Brunei, during the Indonesian Confrontation (Borneo operations, 1963-66) and the results there paralleled my experiences in Malaya

(1955-58). Medical officers in Borneo operations soon became familiar with the protean manifestation of this disease and skilled in its early clinical diagnosis: and quickly came to recognise the diagnostic significance of the characteristic Herxheimer-like reaction designated the diagnostic penicillin-leptospiroal response in Malaya several years previously (Mackay-Dick and Robinson, 1957).

I continued my study of leptospirosis, its early clinical diagnosis, treatment and prevention whilst the Assistant Director of Medical Services (i.e. the Senior Medical Appointment) Headquarters Land Forces Borneo on the last year of Borneo operations. There I visited all positions by air, mainly by helicopter. It was in this theatre of operations that I was particularly impressed with the significance of leptospirosis as a military hazard when 43 per cent of a patrol were struck down with leptospirosis necessitating their withdrawal from an important operation. The human enemy in this theatre of operations had never succeeded in doing this. It was evident therefore that not only commanders at all levels, with special reference to platoon commanders, but all ranks should be briefed on sources of infection and their avoidance where tactically possible, together with all appropriate preventive measures, and evasive action, bearing in mind that the military situation may demand special exposure to this disease which must be accepted as a calculated risk in a necessary military operation. It was in such circumstances that there was a demand for some form of chemoprophylaxis e.g. oral penicillin which has a low incidence of hypersensitivity reactions, or a multivalent vaccine containing the fewest possible

serotypes and having a broad antigenic spectrum.

There is much to be learned from the experience of medical officers of the Royal Army Medical Corps in the realm of leptospirosis not only in Germany but in Hong Kong, Malaya (now Western Malaysia), Singapore, Eastern Malaysia (Sabah and Sarawak) and in Brunei.

It is to be hoped that the lessons from these experiences are to be an exception to the Hegelian view that peoples and governments have never learned anything from history or acted according to its lessons. In other words:

'Those who ignore
the lessons of history
are condemned
to repeat them'

George Santayana.

HISTORICAL.

Leptospirosis was suspected in the Malay Peninsula, now Western Malaysia, for several years before its presence was established by Fletcher in 1925. Since then reports have been made, among others by Galloway (1926), Fletcher (1928), Lewthwaite (1929), in the annual reports of the Institute for Medical Research, Malay (1926, 1928 and 1929) by Danaraj (1950), Mankikar (1951), Robson (1952), Broom (1953), Hughes (1954), Trimble (1954, 1955 and 1956), Fairburn and Semple (1956), Levis (1956), Robinson and Kennedy (1956), Mackay-Dick and Robinson (1957), Mackay-Dick and Robinson (1959a), Mackay-Dick and Robinson (1959b), McCrumb et al. (1957), Russell (1958) and Turner et al. (1959).

The significance of South East Asia as an important focus of epidemic and endemic leptospirosis in man and animals was recognised mainly as a result of intensive investigation by Dutch workers in Indonesia (Walch-Sorgdrager, 1939). Eighteen of the currently recognised distinct antigenic strains of leptospires were initially recognised in Indonesia (Collier, 1948).

Studies of Malayan leptospirosis by British and American investigators in 1951 and 1952 revealed a high prevalence of leptospiral antibodies in human beings, domestic animals and wild rodents and drew attention to rural, urban and forest foci of infection (Wisseman et al. 1955). Based upon stable and specific antigenic characteristics as revealed by the agglutination-lysis reaction, members of the genus leptospira have been classified into

sero groups, comprised of serotypes, sharing major antigenic components (Wolff and Broom, 1954). By definition, a serotype includes all strains indistinguishable one from the other on the basis of cross-absorption procedures. In addition serological and cultural studies indicated the presence of a multiplicity of leptospiral serotypes in Malaya (Alexander et al., 1955).

From the end of 1953 onwards through 1957 and 1958, outbreaks of leptospirosis in British Security Forces in Malaya as well as sporadic cases of this disease in military and civilian personnel were jointly investigated by the United States Army Medical Research Unit and the Institute of Medical Research, Kuala Lumpur, Malaya and by personnel of the Royal Army Medical Corps in collaboration with the late Dr. John Broom of the Burroughs Wellcome Institute, London. The clinical, epidemiological and laboratory diagnostic aspect of these studies have already been reported. (Robinson and Kennedy 1956; Trimble 1954 and 1956; Levis 1956; Mackay-Dick and Robinson 1957, 1959a, 1959b; McCrumb et al., 1957). 'Mass' infections of leptospirosis during the Malayan emergency, (1948-61) have been reported, for example by Campbell 1952 (personal communication) and Worthington 1967 (personal communication). These and other experiences of leptospirosis in Malaya (now Western Malaysia) were repeated by medical officers of the Royal Army Medical Corps in Eastern Malaysia (Sabah and Sarawak) during the Indonesian Confrontation (1963-1966).

Work of outstanding value regarding epidemiological problems of leptospirosis in Malaysia has been carried out by Baker (1962 and

1967 - personal communications) and Baker, 1965. Not only has he increased our awareness of this disease, preventive measures and their application but also its potential as a military hazard in the jungles of Malaysia particularly on active service.

It is acknowledged that the concentration of leptospirosis is greatest in Malaysia and Indonesia (Lancet 1960). Because of the isolation in Weil's disease of icterohaemorrhagiae by Japanese (Inada et al. 1916) and German workers (Hubener and Reiter 1916; Uhlenhuth and Fromme 1915) there has been an unfortunate tendency for Weil's disease and leptospirosis to be regarded as being synonymous. Nothing could be further from the truth and it is felt that is why cases of leptospirosis have been overlooked so often in the past. We know that in Malaysia leptospirosis is normally a mild disease and probably anicteric in at least 90 per cent of cases whilst 'Weil's disease' conjures up in the mind a clinical picture of a seriously ill patient with jaundice, haemorrhages, albuminuria, cylindruria and oliguria and serious renal failure.

Another popular misconception is that the local population in Malaysia do not acquire leptospirosis. Turner et al. (1959) found definite serological evidence of leptospirosis in about 21 per cent of 130 cases of undiagnosed pyrexia. In addition McCrumb et al. (1957) showed that leptospirosis accounted for 13 per cent of the illnesses in 238 adult male Asian civilians investigated for the cause of pyrexia of uncertain origin. Furthermore, Doleman (personal communication 1967) when regimental medical officer of the Malaysian Rangers, formerly Sarawak Rangers and almost Ibans to

a man, saw several cases of leptospirosis among them in Sarawak and some of these cases were severe. Subclinical cases occur (Army Medical Department Research Project 14, No. 132, 1966 - personal communication). Nevertheless it is suggested that the true incidence of leptospirosis in the jungle dwellers in Eastern and Western Malaysia could be assessed by routine serological studies among them; and it would be of special interest to have controls from city dwellers.

Much has been learned regarding leptospirosis in the army since two gunners in Malta who had bathed in the muddy part of the Grand Harbour fell ill, within 10 days, with classical Weil's disease - then unrecognised - and one case was fatal (Marston 1863); yet Baker (1965) could find no evidence of leptospires in shore swamps of the tidal portions of two Malaysian rivers.

GEOGRAPHICAL.

In the literature reference is made to Malay, Federated Malay States and Borneo. In view of the recent political history the present position regarding these territories requires to be stated.

Malaya (now Western Malaysia) formerly the Federated Malay States (FMS), was granted her independence by Great Britain in 1957 when she became a sovereign state. On 16th September, 1963, Sarawak and British North Borneo (renamed Sabah) opted to become part of Greater Malaysia and together comprise Eastern Malaysia. In between lies the oil rich Sultanate of Brunei which remains voluntarily under British protection. These three states occupy the northern part of the island of Borneo (the third largest island in the world), the remaining two-thirds of which is part of the Republic of Indonesia and known as Kalimantan (Fig.1). To facilitate civil administration Sarawak (capital Kuching), is divided into five administrative divisions, numbered from one to five, and Sabah (capital Jesselton) into four Residences, Interior, West Coast, Sandakan and Tawau.

CLIMATE AND TOPOGRAPHY.

This is typically tropical. Temperature and humidity are always high, there is heavy rainfall and where the land is not mountainous it is mainly swampy. There are vast areas of primary jungle and these areas are typical tropical rainforest, the feature of which are those of tall trees, 250 feet high with six layers of canopy formed by lesser trees beneath them so that only rare spots

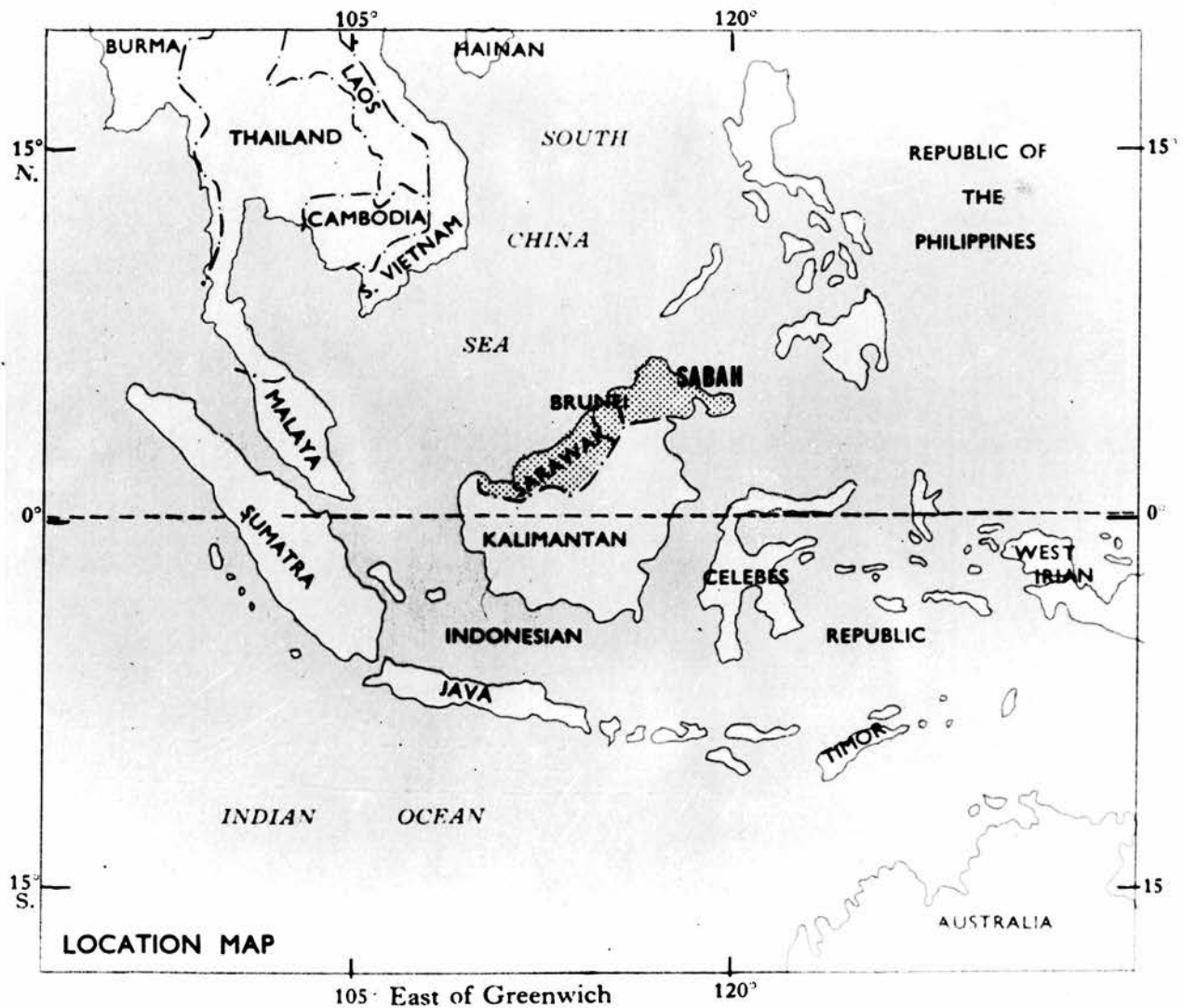


FIG. 1.

Map showing Malaya (Western Malaysia), Brunei, Eastern Malaysia (Sabah and Sarawak) and other countries of South East Asia. Singapore at the tip of the Malaya Peninsula is missing from this map.

of sunlight reach the ground to move a short distance before being caught again by higher branches (Fig. 2). Clouds move through the forest regularly maintaining a constant moisture. (Baker 1965). In addition there are several large rivers, fast flowing in their upper reaches, innumerable small rivers and streams all of which may rise quickly following characteristic tropical rainfall and these water obstacles the soldier must negotiate on active service and during normal jungle warfare training (Fig. 3). In Europe and in deserts the soldier marches on his feet but in the jungles of Malaysia water obstacles are frequent and to be able to swim (Fig. 4) is as necessary as to be fit to march.

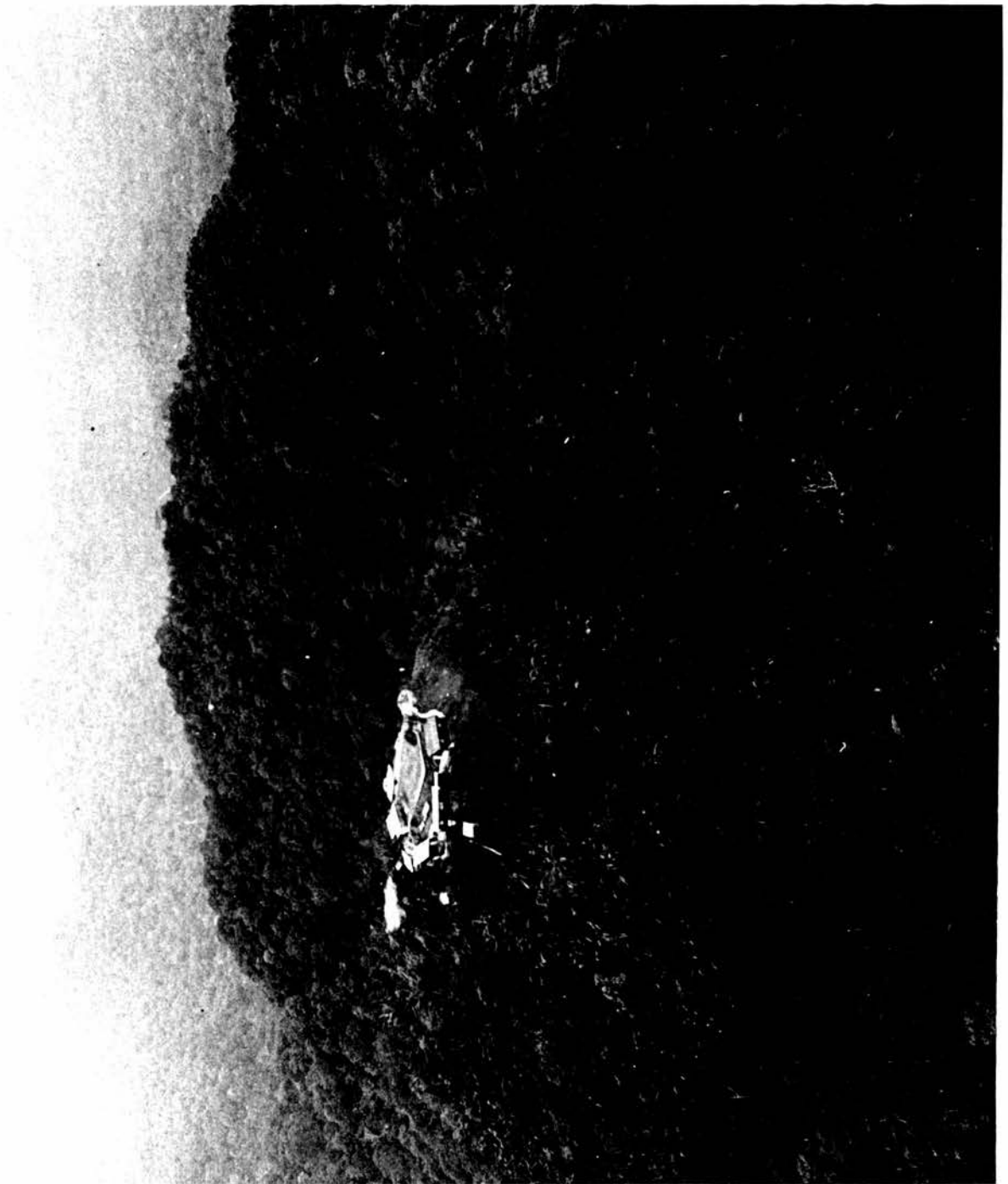


FIG. 2.

Mountain ranges covered by primary jungle showing a radio relay station hacked out of the jungle by British soldiers and supplied entirely by air.



FIG. 3.

River crossing. This patrol on active service in Borneo operations faces the constant threat of leptospirosis.



FIG. 4

A deep fast flowing river. Note the thick vegetation down to the bank. The first Gurkha across stands guard while the remainder of the patrol cross with their equipment.

AEROMEDICAL CASUALTY EVACUATION.

During the Indonesian Confrontation (1963-66) all casualties, from all forward positions, whether from sickness, accidents or enemy action were evacuated by air, mostly by helicopter, (Fig. 5) to base medical installations in Sabah, Brunei and Sarawak, and thence as indicated by long range air transport to Singapore via Labuan Island (Sabah) or Kuching (Sarawak).

Cases of impending renal failure, in Eastern Malaysia, due to leptospirosis were evacuated to a renal dialysis unit in Singapore either from Labuan Island or Kuching; some of the distances involved in aeromedical casualty evacuation were as follows but when miles are measured in flying hours we were closer to Singapore than parts of the United Kingdom to specialised medical centres.

Tawau (Sabah) to Labuan Island (Sabah)	: 200 miles (1 hour)
Labuan Island to Kuching (Sarawak)	: 425 miles (2 hours)
<u>Kuching to Singapore</u>	: 440 miles (2 hours)
Jesselton (Sabah) to Brunei	: 110 miles ($\frac{1}{2}$ hour)
Brunei to Labuan Island	: 35 miles (20 mins. by helicopter)
Sibu (Sarawak) to Kuching	: 130 miles (35 mins.)
<u>Labuan to Singapore</u>	: 745 miles ($3\frac{3}{4}$ hours)

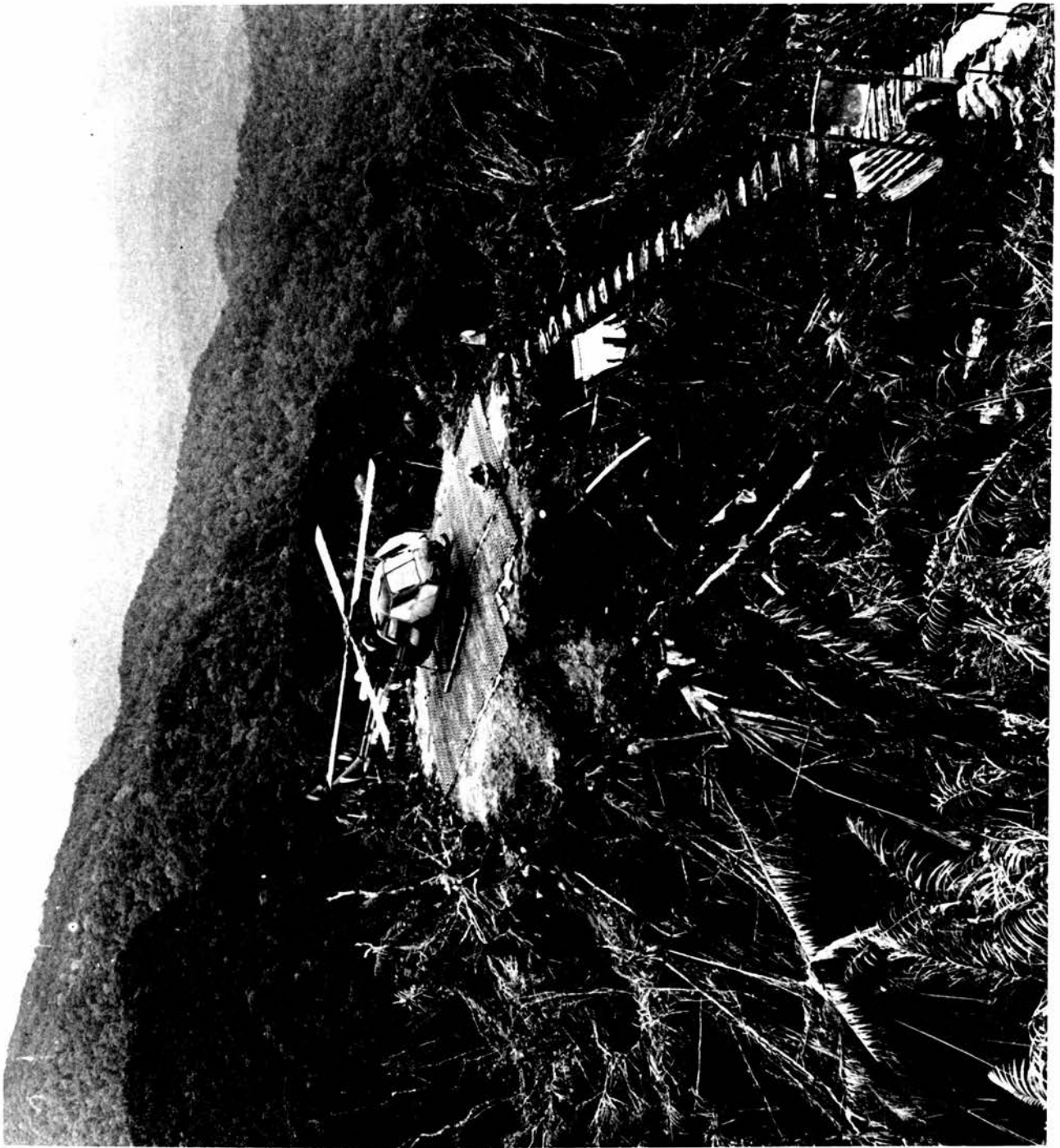


FIG. 5.

One of the hundreds of helicopter landing pads hacked out of primary jungle in the mountain ranges of Eastern Malaysia.

EPIDEMIOLOGICAL PROBLEMS OF LEPTOSPIROSIS.

Leptospirosis is a zoonosis carried by wild vertebrate animals, particularly rodents and has been described as probably the world's most widespread contemporary zoonosis (Van der Hoeden 1964). The ideal hosts are those that are readily infected and yet remain healthy and that excrete leptospirae in the urine for long periods - such animals as rats, voles, field mice, hedgehogs and shrews, are responsible for maintaining and transmitting the infection. The organisms localise in the kidneys in the epithelium of the convoluted tubules and periodically are washed out in the urine thereby contaminating the environment. Other wild animals, hares, foxes, skunks, opossums, bandicoots, civets, etc. and domestic animals, cattle, horses and pigs may become infected through grazing on pastures contaminated by the reservoir hosts. These secondary hosts unlike the primary ones may or may not suffer from the infection. At a later date they too may excrete the organisms in the urine for short or long periods and so add to the infection in the environment.

Man becomes infected either indirectly through contact with urine-contaminated soil and vegetation or through immersion in, or ingestion of, infected water or directly through tending infected domestic animals, i.e. dogs as well as by handling mice or rats (Coghlan 1967 - personal communication). Reptiles, water birds and possibly other forms of life are suspect in the spreading of this disease (Control of Communicable Disease in Man 1960 and 1965) as are also ticks and other bloodsucking insects and helminthic

parasites (WHO Chronicle 1968).

Leptospirosis is an occupational hazard affecting among others sewer workers, farm workers, coal miners, people who clean fish, handlers of flesh of sick animals, certain laboratory workers, paddy field workers, cane sugar workers, animal contacts, kennel personnel, construction workers, forestry and surveying workers (Turner 1969).

Modes of Transmission:

The leptospire may enter the body through the skin (especially if wounded, macerated or diseased), the nasal and buccal mucosa, conjunctiva, genitalia or anus. The bite of an animal, particularly a small animal such as a rat or a mouse, may provide a portal of entry particularly as they tend to urinate at the same time and so contaminate the wound. Venereal transmission may occur in humans (Turner 1969). It has been suggested that leptospirosis may be spread by the transplacental route to the foetus in utero (Chung et al., 1963) and so be a cause of abortion in humans as it is in pigs. Lawson, 1969 - personal communication - reports that in one area of Scotland leptospirosis in the pregnant sow was causing poor litters due to abortions but since penicillin has been given to pregnant sows there has been a dramatic drop in the incidence of abortions among them.

From time to time there have been reports of acute outbreaks of human leptospirosis associated with epizootics in wild or domestic animals in special environmental conditions. Such outbreaks have

occurred principally among rice-field workers, cane-cutters, butchers, field workers and other occupationally exposed persons. The cycles of such outbreaks appear to be linked with the ecology of animal hosts and their environment (WHO 1967). In Sarawak, Telford (1966) maintained graphs indicating the monthly incidence of disease in security forces. The number of troops in the theatre of operations remained constant but there was an obviously higher incidence of leptospirosis during the very wet months; when of course there would be more floods.

The factors that contribute to the formation and maintenance of water foci are imperfectly understood. Some of the conventional ideas of the potential infectiousness of stagnant waters and slow-moving streams in endemic foci were not necessarily valid in different ecological foci of infection. For example the infectiousness of rapidly flowing water in jungle (and other) foci of infection has been demonstrated (WHO 1968). Moreover, the infectiousness of these waters increases at the time of flood (Baker 1965; WHO 1968).

Survival of Leptospire:

Factors which favour the survival of virulent leptospire outside the bodies of susceptible vertebrates include moisture, warmth and pH values of soil, and surface waters, around neutrality but to date it has not been found possible to determine any safe or 'cut off' pH levels. (Baker and Tigert 1967 - personal communication). As regards warmth Coghlan (1967 - personal communication) has reported a case of leptospirosis in a man who fell into the Braid Burn in

Edinburgh on Hogmanay. Adverse factors include salinity, but not necessarily NaCl for this chemical is essential for growth of leptospire under laboratory conditions, chemical pollution and dessication. (Tigert and Baker 1967 - personal communication; Turner 1969).

Infectivity of Water:

Leptospire do not multiply in water; and their length of life there is not known but it is certainly dependent on several factors, e.g. the presence of plankton and ciliates as well as the acidity of water. In any case leptospire die off at 1 or 2 logs. per day even in the most suitable water. This must influence the infectivity of any water, particularly water in large reservoirs, lakes or ponds, which may be fed from streams, where the dilution factor is great. (Baker and Tigert 1967 - personal communication).

Water Infectivity:

The reservoir for leptospirosis is the stream or river bank: and it has been shown that there is 100 to 200 times increase in infectivity of a stream during spate compared with the infectivity of the same stream during normal flow. (Baker and Tigert 1967 - personal communication). A lake, pond or reservoir may normally be safe for bathing at least 24 hours after flood waters have run into it because of the dilution factor and the 1-2 logs. daily decrement of leptospire. Such waters are safer for bathing than a stream and certainly safer than a stream in flood: (Baker and Tigert 1967 -

personal communication) but on all occasions contact with the banks and soil are to be avoided.

THE OPERATIONAL HAZARD OF LEPTOSPIROSIS TO THE SOLDIER.

Water is a vector of this disease to man and the soldier in jungle operations is necessarily variously exposed to it. (Figs. 6 and 7). Baker (1965) has shown that for occasional brief periods streams following rainfall and flooding have been found to be far more infectious than the swamp. This suggested a hypothetical reservoir of leptospirae that was washed out by the flood. (Fig. 8). Investigations revealed a frequency and intensity of infectiousness in the shore sand which explains the infectiousness of the flooded stream. Baker (1965) also established that foci of high infectiousness could be found along the smallest tributaries high on the forested mountain sides, and the generalised leptospiral contamination of the Malaysian tropical rainforest.



FIG. 6.

Ever vigilant for the terrorists, a patrol moves through a swamp in Malaysia.



FIG. 7

Men from an Infantry Regiment recover stores from a river in Eastern Malaysia following an off-centre air drop.



FIG. 8

A patrol making its way along a jungle stream in Malaysia. Note the shore sand which is a reservoir of leptospire and which are swept out during flooding when flood waters are highly infective.

MEDICAL INTELLIGENCE.

In preparing a guide for regimental officers on leptospirosis, its cause, sources of infection, modes of infection and prevention, its incidence and military significance, we should bear in mind that in the Malayan Emergency (1948-61) McCrumb et al. (1957) showed that 35 per cent of all febrile illnesses among military personnel were due to leptospirosis, and that 40 per cent of all febrile illnesses which were not malaria were due to leptospirosis; also that in the daily observation of one battalion the amount of leptospirosis was directly correlated with the amount of jungle duty; that on the average there was approximately one case of laboratory proved leptospirosis per battalion per day of jungle duty, while four out of five cases were men who had been on jungle duty in the two weeks prior to onset (Lancet 1960; Baker 1965). On the other hand Mackay-Dick and Robinson (1957) found that 96 per cent of 84 laboratory proved cases of leptospirosis in soldiers first reported sick within 10 days of returning from jungle patrol. The remainder were living in jungle camps. It will therefore be seen that in the provisional diagnosis of leptospirosis in service personnel their movement or locational history is of much significance. Of course, in the army, territorial/residential/occupational history has always been a most important aspect of patient examination. Where have you been? What is your occupation and its hazards and what are your hobbies and recreations are stock questions.

By the optimum use of existing knowledge regarding leptospirosis, its sources of infection and modes of transmission, exposure to it can be lessened and so may the incidence of this disease on active service in the Malaysia tropical rainforest.

FACTORS FOR CONSIDERATION.

These include:-

- (a) there is no ready way of determining whether a pool, lake or river is safe to bathe in because of its pH or chemical content.
- (b) water will definitely be free from leptospires only when a free chlorine content can be demonstrated as for drinking water.
- (c) streams in spate are always to be avoided but water from them at basal levels or at least six hours after flooding may be used, as a calculated risk for ablution purposes or for the washing of clothes.
- (d) pools or lakes for bathing are always to be used in preference to streams in any state.
- (e) control over bathing sites is a sine qua non.
- (f) whilst preparing for bathing there should be no sitting on the ground or walking barefoot; and every opportunity should be taken to use rocks, wooden or bamboo platforms to avoid contact of the skin with soil or sand.
- (g) the water of mining pools for bathing and washing of clothing may be considered as long as the drain free edge of the pool is used but nevertheless some platform approach to the water is

advisable.

- (h) the tidal portions of rivers have been found to have little leptospirosis potential but scrub typhus is a danger wherever there is a lalang, scrub or forest on the bank.
- (i) the risk of leptospirosis is ever present but it is necessary to balance the relative risks against operational needs as well as morale and the hygiene of the body (Baker 1962 - personal communication; Baker and Tigert 1967 - personal communication).

Medical advice may conflict with military requirements and the commander must be fully briefed before taking the decision involving a calculated risk, but it is in such circumstances of special risk to leptospirosis with special adverse consequences on combat effectiveness that oral penicillin may be of value prophylactically.

Where possible streams should be crossed when not in flood or not until six hours at least after flooding and then only at their narrowest point and shallowest depth, with no splashing and water not to come in contact with the bare skin, nasal or buccal mucosa or conjunctiva; while immersion in whole or in part is particularly to be avoided.

Where a river is in spate and a weapon is dropped then in view of past experience of the high incidence of leptospirosis from repeated diving to retrieve it, the patrol commander is left with three possible lines of action, namely accept the weapon as lost: only 25 per cent of the patrol to endeavour to retrieve it by repeated diving and to be given abortive treatment with oral

penicillin or oral terramycin: or the entire patrol to endeavour to retrieve the weapon(s) by repeated diving and all to take oral penicillin. Whether or not oral penicillin should be ordered prophylactically would depend on the day of the patrol and its further duration bearing in mind that the incubation period of leptospirosis may vary from 4 to 21 days.

At this point it may be of interest to record that in one patrol in Sabah there was one case of leptospirosis which was of such severity that he was flown to Singapore for renal dialysis. He was on the very seriously ill list but happily he recovered. Later I met his patrol commander who said that this soldier was the only one to go bathing in untreated water on patrol - a statement of significance. To cap this story is the fact that in a very well disciplined base camp in Tawau, Eastern Malaysia, the only man to acquire leptospirosis was the water duty man, in other words the only person who had an excuse for coming in contact with 'raw' or untreated water.

Here it may be appropriate to recount the following anecdote. In Malaya (now Western Malaysia) a British officer, his wife and two sons, the latter on vacation from the United Kingdom went on a picnic with all bathing attire. The husband put on his bathing trunks but in the highest traditions of the British Army did not bathe in the river as his Divisional Standing Orders stated explicitly that this was forbidden; but he did sit on the moist river sand bank whilst his sons dived in to a river pool from the riverbank. His wife, who had just started a monthly period, decided not to bathe so sat

knitting in a chair in the shade by the river. The sequel to this was that father who did not bathe but who sat on the damp river sand acquired leptospirosis but not the sons or their mother.

GENERAL PREVENTIVE MEASURES.

Such measures include:-

- (a) destruction of, and prevention of access to, rodents.
- (b) food and anything edible to rats and that includes toilet soap, should be kept secure from rats and their urine. Rats will eat anything - even the binding on the handle of a squash racquet.
- (c) destruction by burning, or chemicals, of leptospirae excreted in urine of rodents or domestic animals.
- (d) use of waterproof boots and protective clothing. The soldier's jungle clothing and boots may be of relative protective value (Fig. 9).
- (e) hot water and soap for hand washing.
- (f) antiseptic first-aid treatment of cuts and abrasions.
- (g) water for hosing equipment not to come in contact with the skin.
- (h) footgear should be protected from crawling, swimming or climbing rodents and also, like food or anything edible, be kept under a solid cover impermeable to urine, when not in use.
- (i) avoid sitting on the unprotected ground and walking with bare feet.



FIG. 9

Members of a patrol construct a temporary shelter in the jungle.
Note: Headdress, cravat, shirt with long lacing canvas and rubber
jungle boots.

The troops lived in, and patrolled from, company positions in the jungle for a matter of months (Fig. 10 and 11) and they declared war on rats with poison and traps with gratifying results. Cats are clean animals and do not foul the ground and I suggest that a significant number of 'wild' domestic cats, which I remember well as a boy in the Highlands of Scotland, in each company position may be of significant value in rodent control. If suitably bred and trained such cats avoid personal contact with humans and so do not readily become pets.

No practical measures will eliminate all cases of leptospirosis but once a measure is recognised to be of value in controlling one particular factor of contagion, this should simplify the search for other factors. (Baker 1962 - personal communication).

Every opportunity should be taken to collect rain water for ablution and laundering purposes and keep it free from leptospiral contamination. In circumstances of special need in Borneo where pumps and filters had become temporarily ineffective, some company positions managed admirably with rain water for such purposes.

Patrol commanders have a special need to know the extremes of the incubation period (4-21 days) of leptospirosis vis-a-vis the remaining duration of the patrol and the threat to combat effectiveness by leptospirosis after circumstances of special exposure when 43 per cent or more may be rendered hors-de-combat by this disease.



FIG. 10

A forward position in Sarawak, the soldier's home in the jungle from which he patrols. An aerial view showing the type of terrain.



FIG. 11

Another example of the soldier's home in the jungle - a defended position in the jungle from which patrols are carried out.

VACCINATION.

Vaccination has been considered successful in the Italian rice fields (Babudieri 1957) where those at risk are concentrated at work, but differences in types and more variable exposure have operated against its effectiveness, and indeed use, elsewhere. Nevertheless in areas where multiple leptospirosis occurs efforts should be made to develop multivalent vaccines containing the fewest possible serotypes and having a broad antigenic spectrum (WHO 1967).

WHEN IS IT SAFE TO BATHE IN FRESH WATER?

One example where this question was most pertinent was in Sarawak in what was known as the Bau Lake (Fig. 12). This is said to be a 200 feet deep gold mine, flooded by a spring in its base, widely exposed and unprotected from the sun, in the first Division of Sarawak. It is almost certainly non-infective solely on account of its size, dilution factor from any contaminating flood water and the daily decrement of any added leptospire; and not from any pH or chemical content factor. In fact it was used as a lido which included the following facilities, namely a wooden platform extending from the bank together with a springboard, a chute the summit of which was reached by a ladder on the bank so that individuals would slide straight into the water, also a covered raft pulled to the bank by



FIG. 12

Bau Lake in Sarawak, showing exposed position, wooden platform, spring board, shute and the floating covered raft with rope to the bank.

a rope on which individuals could embark. It could then be rowed well away from the bank and used for diving purposes. Accordingly there was no contact with the damp part of the bank or with the bottom of Bau Lake due to its depth. We therefore turned a blind eye to this bathing pool particularly for the good reason that no cases of leptospirosis had been traced to it during the period of the Indonesian Confrontation (1963-66).

In retrospect I feel that I was too strict in advising no bathing in a pool in Serian in Sarawak when much less than a calculated risk would have been involved by bathing at least 24 hours after flood water had flown into it particularly if a wooden landing stage and springboard had been used and the bank carefully avoided; also if plimsolls had been worn throughout. Nevertheless if somebody's son had acquired leptospirosis, with jaundice, haemorrhages and anuria with fatal results one would have felt morally responsible. It is the duty of the medical officer to advise commanders at all levels on all matters affecting the health of the troops and so if a calculated risk is to be taken for recreational bathing it is for the individual to take it on his own responsibility fully alive to the situation and with the approval of his commander.

The work of the United States Army Medical Research Unit in Malaya and of the Royal Army Medical Corps in Malaya during the Malayan emergency (1948-61), and of the Royal Army Medical Corps in Sabah and Sarawak during the Indonesian Confrontation (1963-66) has pinpointed leptospirosis not only as an occupational hazard of

soldiers on active service in the jungles of Greater Malaysia but as a hazard of military significance e.g. 13 members (or 50 per cent) of a patrol of 26 on completion of a jungle patrol fell ill almost simultaneously with leptospirosis (Campbell 1952 - personal communication); 30 (or 43 per cent) out of 70 Gurkha all ranks became ill with leptospirosis - casualties from this disease appearing 7-10 days after the beginning of jungle duty against communist terrorists (Worthington 1967 - personal communication).

THE SPECIAL HAZARD OF LEPTOSPIROSIS IN RIVER CROSSING.

The regimental medical officer of a Highland regiment in Sarawak (Weeks 1966 - personal communication) reported that two platoons went in hot pursuit of the enemy during an enemy incursion. The fastest means of covering the ground - especially at night - was to wade upstream. They spent a total of about 12 hours in the water, immersed to the knees, and occasionally up to the neck. The water level was high. The stream passed through uninhabited jungle. Five days later the first case of leptospirosis appeared. The final count was 15 cases out of 52 all ranks (i.e. 29 per cent) taking part in this patrol (Moorhouse 1966 - personal communication): a patrol of 21 Royal Marine Commandos were crossing a river in spate in Sarawak, two weapons were dropped and the men dived in relays over a period of four hours in an endeavour to retrieve the lost weapons. The first man to go sick with leptospirosis did so on the ninth or tenth day

following the incident. When the sixth case fell sick the Commanding Officer of the unit decided that he must visit them and with the possibility of further cases occurring making the troop ineffective, he had no alternative but to order the patrol to return to base. In all there were nine cases of leptospirosis in this patrol, i.e. 43 per cent of 21 all ranks. Leptospirosis had achieved what the Indonesians had never achieved. (Taplin 1966 - personal communication). A platoon of Gurkhas with a similar experience to these commandos had a high incidence of leptospirosis resulting - 25 per cent fell ill with leptospirosis but, as many were not strong swimmers, it is fair to suggest that the number falling ill were a much higher percentage of those who spent much time diving to retrieve the lost weapon. (Telford 1966 - personal communication). Likewise Brodie (1966) in a personal communication reports that in South East Sabah in 1964 a patrol consisting of one officer and five men were ferrying across a tributary of the Serudong river, which was in spate, when the raft overturned and all six were thrown into the river. They all reached the bank. The officer and two men who were powerful swimmers stripped off and recovered as much of the ammunition and as many of the weapons as they could while the other three watched. The officer and the two men who were immersed in the water for a considerable period developed fever, eventually diagnosed as leptospirosis. The other three who were immersed only for a short period were unaffected. This represents an incidence of leptospirosis of 50 per cent of those who were immersed in the water, but really 100 per cent of those who had prolonged immersion and were unclothed

at the time. We had numerous other instances where a significant percentage of cases of leptospirosis on jungle patrol followed the sequence of river crossing, river in spate, dropped weapon(s), repeated diving of the patrol over a period of hours to retrieve the dropped weapons, e.g. 19 per cent of one patrol and 30 per cent of another patrol.

Training in river crossing by soldiers was also a hazard. Out of 105 men practising river crossing, eight fell ill within a few days with leptospirosis. The Commanding Officer said that such a casualty rate was unacceptable and could we not give his men 'something to take' during periods of special exposure to leptospirosis? It was decided that in training, periods of special exposure to leptospirosis could normally be avoided but not so on active service when the patrol could be rendered ineffective due to leptospirosis casualties without contact having been made with the human enemy. One such operational report is as follows (Taplin 1966):

Quote:

LEPTOSPIROSIS - SARAWAK OPERATIONS.

Reference: A. LFB 1220/3 Med dated 6th June, 1966.

B. 40 RM 13/5/8 dated 12th June, 1966.

1. Reference B. gives the outline facts concerning a patrol of 'A' Company of this Commando in Sarawak during late October and early November, 1965.
2. This letter in amplification shows the problem which arose from the operational angle.
3. 3 Troop were on patrol in the border area near Plaman Mapu - in

- the Serian district of the 1st Division. When crossing a river two rifles were dropped in the water. After all 21 members of the patrol had dived in relays, the weapons were recovered.
4. As the patrol was still close to base they returned and after drying out - resumed their patrol the next day. They returned after 5 days - all men still being fit. On the 9th or 10th day after the incident one man went sick and on the following day two further men became ill. They were seriously sick and needed evacuation.
 5. No further cases occurred during the next two days and I decided that an important patrol operation should commence. This operation involved 3 Troop and another sub-unit and was designed to last up to eight days in an extremely remote area from which casualty evacuation by helicopter would be very difficult indeed.
 6. It was appreciated that further cases of leptospirosis might occur in 3 Troop and the patrol was therefore ordered to lie up in a forward base for 24 hours to see if any did so. The march to this forward base was very hard going and during it, two men did become ill. There was a helicopter landing zone at the forward base and they were evacuated by helicopter. This was on the 14th day after exposure.
 7. That night a further man went sick. This made a total of six to date. Included were two junior non-commissioned officers. With the possibility of further cases occurring - making the troop ineffective and with the problem of evacuation once the

patrol had moved from the forward base - I had no alternative but to visit them and order them to return to Plaman Mapu.

8. On the 16th day after exposure - a further man went sick and one more on the 18th and 21st days. This brought the total to 9.
9. Even a mild case of leptospirosis makes a man unfit for active patrolling for several weeks. For some time after apparent recovery he is liable to have a relapse if he takes violent exercise. (This refers to cases not treated with penicillin).
10. I am certain now that preventive medical treatment must be given as soon as possible after any man has been exposed to conditions which are known to be potential leptospiral sources.

Unquote.

An extract from Reference B. to that report and referred to above is as follows (Garrod 1966 - personal communication).

Quote:

LEPTOSPIROSIS.

- (a) The river was 5 feet deep, and it was in spate after a dry period of weather.
 - (b) Every man on the patrol of 21 was equally exposed.
 1. The men dived in relays for the weapons.
 2. The diving lasted for four hours.
 3. The men were fit and rested.
- (a) They had left the company base on this day to start

the patrol.

(b) They had patrolled about 5 miles.

4. The men had been wet about two hours before the incident.

5. They continued wet for a further two hours, having no dry clothes.

(c) The final count of cases we believe to be 9.

Unquote.

ABORTIVE TREATMENT AND CHEMOPROPHYLAXIS IN CIRCUMSTANCES
OF SPECIAL EXPOSURE TO LEPTOSPIROSIS.

Turner (1969) recommended that abortive treatment should be considered in cases of special exposure to leptospirosis.

We have already outlined the high incidence of leptospirosis which may occur on jungle patrol when for example 43 per cent of an important patrol were rendered hors-de-combat by this disease resulting in the entire patrol being rendered ineffective and having to be withdrawn. We recommended that in all such circumstances of special exposure penicillin should be given prophylactically to all members of the patrol so exposed. There was much discussion as to whether penicillin should be given parenterally or orally. At this very early stage of the infection it was felt that there would not be sufficient leptospire in the body to cause a significant penicillin-leptospiral reaction.

Following river crossing training by a company of an infantry battalion there were several cases of leptospirosis. The Commanding Officer was most concerned with this and said that as he could not accept such a number of casualties during training could we not give his men so exposed a drug to prevent the disease. We decided on chemoprophylaxis with penicillin and Telford (1966) reported as follows:

"LEPTOSPIROSIS 1st Bn. BLANKSHIRES.

1. A recent outbreak of leptospirosis in one company of the 1st Bn. Blankshires followed the now familiar pattern.

2. The company of 105 men had been practising river crossing and swimming under operational conditions in the Tebakang area of the first Division of Sarawak for about five weeks.
3. Within a period of five days, eight soldiers developed clinical signs of leptospirosis, all of which were later confirmed by serological investigations. The degree of severity varied from severe to mild, and all are now fit.
4. Although the incubation period varied in the soldiers, it is highly probable that they were all infected at the same time. This would indicate that the infectivity of a river varies from day to day, as these soldiers had been training in the same river for five weeks. The concentration of leptospirosis in the river at any one time is presumably influenced by rainfall somewhat up river.
5. These men are continuing their training in swimming and river crossing in the same river. In order to reduce the chances of being infected with leptospirosis, prophylactic penicillin has been used.
6. Training takes place normally over two lots of five days, then a break, and another period of training. The dosage of penicillin being tried now is 500 mg. of oral penicillin five times during the day. This is being supervised in the same way as Paludrine administration for malaria. The penicillin is taken every day they are training and for a minimum of four days. The first daily dose is taken at 0700 hours, which is half an hour before training starts and the last dose is taken

four hours after training is finished for the day.

7. The question of giving penicillin by injection either as depot or seclophen penicillin was discussed at much length and the administrative difficulties of giving constant injections to these soldiers were considerable. We decided therefore to try the oral penicillin under strict supervision.
8. There are just over 100 soldiers involved in this trial, but there are no controls. The requirement is to keep the company free from infection as far as possible and the role of the company does not really allow us to leave half the company unprotected during their training.
9. We are naturally keeping a close and interested watch on all those soldiers and I shall keep you informed about any developments whether for good or bad.
10. What we are doing is clearly not good medicine but I think it is the only medical solution to a necessary training problem."

There were no cases of sensitivity to oral penicillin which suggests another advantage of the oral route over parenteral penicillin: in addition there were no cases of leptospirosis in those having oral penicillin prophylactically. As hostilities soon ceased we had no further opportunities in Eastern Malaysia to pursue this investigation further.

COMPARISON WITH THE INCIDENCE OF LEPTOSPIROSIS
IN OTHER AREAS OF THE FAR EAST.

The French Indo-Chinese war focused attention on this disease in Vietnam. Three epidemics occurred in the Mekong Delta in 1950, 1951 and 1952; also in one operation in Vietnam 126 men, nearly one quarter of the effective force, were incapacitated by the disease (de Lajudie et al., 1953). Delahousse (1961) published a summary of 153 cases of leptospirosis occurring in military personnel during the operations in Tonkin and Laos between 1953 and 1954. In another report by Spinu et al., (1963) 121 cases of leptospirosis were recorded in North Vietnam among members of a military wood-cutting detail during June and through September, 1959.

An outbreak of 168 cases of anicteric leptospirosis on the outskirts of Chunking, China was reported by Wang et al., (1965). Of interest in this epidemic were the striking pulmonary manifestations. Eighty-three patients had respiratory involvement and four died of asphyxia from massive pulmonary haemorrhage on the third to fourth day of disease. There was no clinical jaundice or renal involvement. I saw two such cases, both fatal, in Malaya before the work undertaken by Mackay-Dick and Robinson (1957).

Also in Indo-China the French (excerpts selected and translated from *Le Service De Santos En Indochine, 1946-1954*) found that leptospirosis was endemic in the Delta areas. Military operation in marshy zones and rice paddies had a high incidence of infection. It was a serious problem in the French prisoners of the Viet Minh (Allen et al., 1968). The French found essentially the same species

of leptospira that were found in Malaya.

To date leptospirosis has not been found by the Americans to be a military problem in Vietnam (Alexander 1966 - personal communication) but it is suggested that it is probably more common than is reported. Allen et al. (1968) in their paper on the clinical picture of leptospirosis in American soldiers in Vietnam predict that 'alert physicians who fully evaluate the non-specific symptom complex of headache, myalgia, conjunctival suffusion and gastro-intestinal complaints - with urinary abnormalities - should be rewarded by making the clinical diagnosis with increasing frequency'.

Buescher 1969a (personal communication) reports that 'leptospirosis has not been a significant problem in American troops in Vietnam. The few scores of cases encountered have been largely anicteric 'aseptic meningitides'. They comprise approximately 10 per cent of the cases admitted as pyrexias of unknown origin, and have been diagnosed retrospectively on the basis of serological examination. Cases of leptospirosis, diagnosed on admission and treated with antibiotics, have been too few to permit evaluation of the influence of antibiotic therapy on the disease as encountered in Vietnam. Because of the paucity of cases encountered, no serious consideration of chemoprophylaxis has been entertained.' The question may be posed why do the American Forces in Vietnam have such a low incidence of leptospirosis (10 per cent of cases of PUO) vis-a-vis the British Security Forces in the Malayan Emergency namely 35 per cent of all febrile illnesses (McCrumb et al. 1957). Our experience is that the amount of leptospirosis is directly correlated

with the amount of jungle duty. Therefore the likely answer to the above mentioned question is that in jungle warfare the British live in defended positions in the jungle for a matter of months and patrol from there; whereas the relatively low incidence of leptospirosis in the United States Forces in the Republic of Vietnam may be directly related to their mode of transport to and from primary battle sites. Patrols commonly commence on high ridges from a forward fire base to which troops are air lifted, rather than at the base of hills or ridges where men must move upwards. While there are no hard facts to establish this firmly, it seems to be a reasonable working assumption (Buescher 1969b - personal communication). In other words the incidence of leptospirosis in British Security Forces in Malaysia and in American Forces in Vietnam is correlated with duration of jungle duty, i.e. with duration of constant exposure to this disease.

LABORATORY DIAGNOSIS.

In all our cases in Malaya (Mackay-Dick and Robinson 1957) the clinical diagnosis was confirmed by blood culture and/or serological tests. Before we left Malaya in 1958 we had treated 140 consecutive laboratory confirmed cases of leptospirosis (Mackay-Dick and Robinson 1959a) on the lines already reported (Mackay-Dick and Robinson 1957). There were no fatal cases and no secondary fever in our series. In Eastern Malaysia (Sabah and Sarawak) during the Indonesian Confrontation (1963-66), cases of leptospirosis were similarly investigated but the diagnosis was self evident within a few hours of early institution of adequate penicillin therapy by the occurrence of the characteristic penicillin-leptospiral response (Mackay-Dick and Robinson 1957 and 1959a).

In the army on active service during jungle patrol a sick soldier may be a serious handicap to the operational effectiveness of the patrol and so he is evacuated quickly by helicopter if at all possible. The laboratory diagnosis takes time and merely serves to confirm the clinical diagnosis.

Gsell (1966), as Mackay-Dick and Robinson (1957) have done, stresses the correlation between the duration of the illness and the effects of adequate antibiotic therapy. If adequate treatment is started on day 5 the peak titres are likely to be low; they will be lower when treatment is started on days 3 and 4; and if treatment is started on days 1 or 2 there may be no detectable antibody reaction during the ensuing weeks. This stresses the need

for obtaining a specimen of blood before antibiotic treatment is given as the only certain means of diagnosing leptospirosis may be isolating the strain from this specimen (Turner 1969). If the blood culture becomes contaminated, as has been my not infrequent experience, then a case of leptospirosis treated early with adequate antibiotic may have a negative blood culture and peak titres not of diagnostic level yet have the characteristic penicillin leptospiral response (Mackay-Dick and Robinson 1957).

CLINICAL DIAGNOSIS OF LEPTOSPIROSIS.

As already suggested the clinical diagnosis of leptospirosis is not difficult in soldiers on active service in the jungles of Malaysia because it is predominantly in the jungles that they acquire this disease (Mackay-Dick and Robinson 1957; McCrumb et al., 1957). The incidence of malaria and of scrub typhus is not significant because of the standard daily paludrine and the routine impregnation of wearing apparel with DMP (di-methyl phalate) together with other 'anti-scrub' drills. Malaria was quickly diagnosed on examination of blood films/thick drops. The regimental medical officers located at Battalion Tactical Headquarters, a defended position in the jungle, had clinical sideroom facilities which included slides, stains and a microscope and were all capable of making a laboratory diagnosis of malaria. As regards scrub typhus the presence of an eschar was diagnostic as was the prompt therapeutic response to terramycin or chloramphenicol; the use of the latter was, of

course, discouraged.

When it is acknowledged that in the jungles of Malaysia any febrile illness characterised by headache, myalgia, conjunctival suffusion and gastro-intestinal symptoms in the presence of urinary abnormalities should be regarded as leptospirosis until proven otherwise (Mackay-Dick and Robinson 1957; McCrumb et al. 1957), it is to be expected that such cases from the jungles of Malaysia are quickly recognised and evacuated promptly by helicopter for early treatment with adequate doses of antibiotic, normally crystalline penicillin parenterally but oral terramycin in cases with a history of hypersensitivity to penicillin.

CLINICAL FEATURES.

The clinical manifestation of leptospiral infection in Malaysia do not differ appreciably from those described by other workers in other parts of the world (Schuffner 1934; Walch-Sorgdrager 1939; Van Thiel 1948; Gsell 1952; Woodward 1953). Clinical pictures vary from a non-specific short term fever with cellular elements and albumin in the urine - although a normal urine may occur (Mackay-Dick and Robinson 1957) - to an illness of varying severity with high irregular fever which falls by lysis from the fifth to the tenth day (Figs. 13 and 14) with many or all of the following features, namely proteinuria, cylindruria, oliguria/anuria, haemorrhages, hepatomegaly, icterus, splenomegaly, lymphadenopathy, rashes, muscle tenderness, headache, myalgia, neck

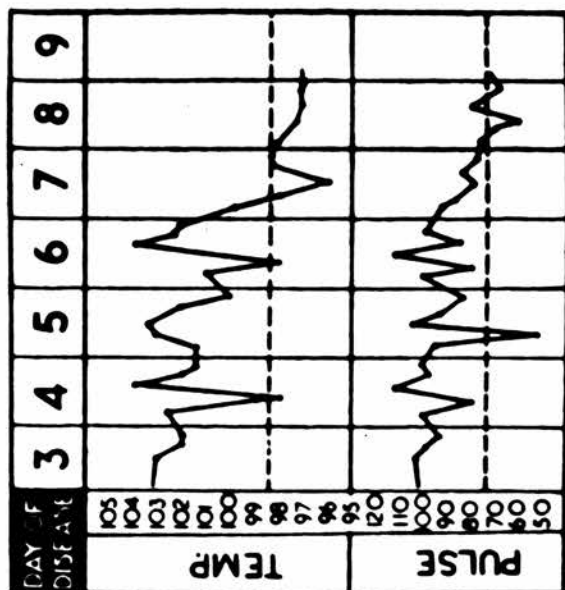
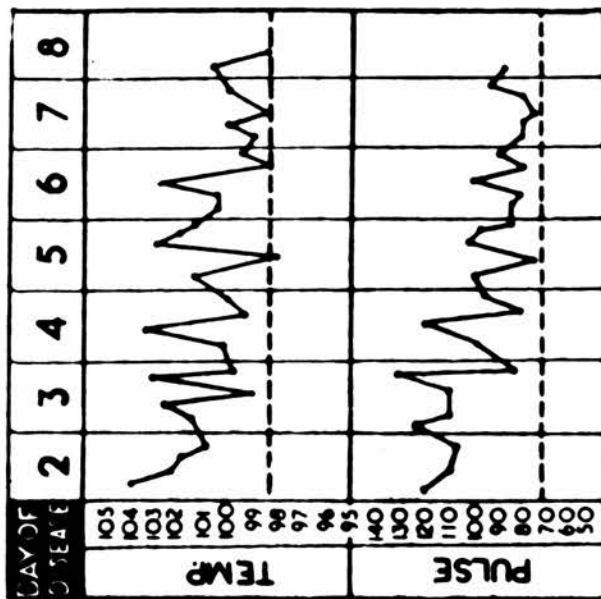
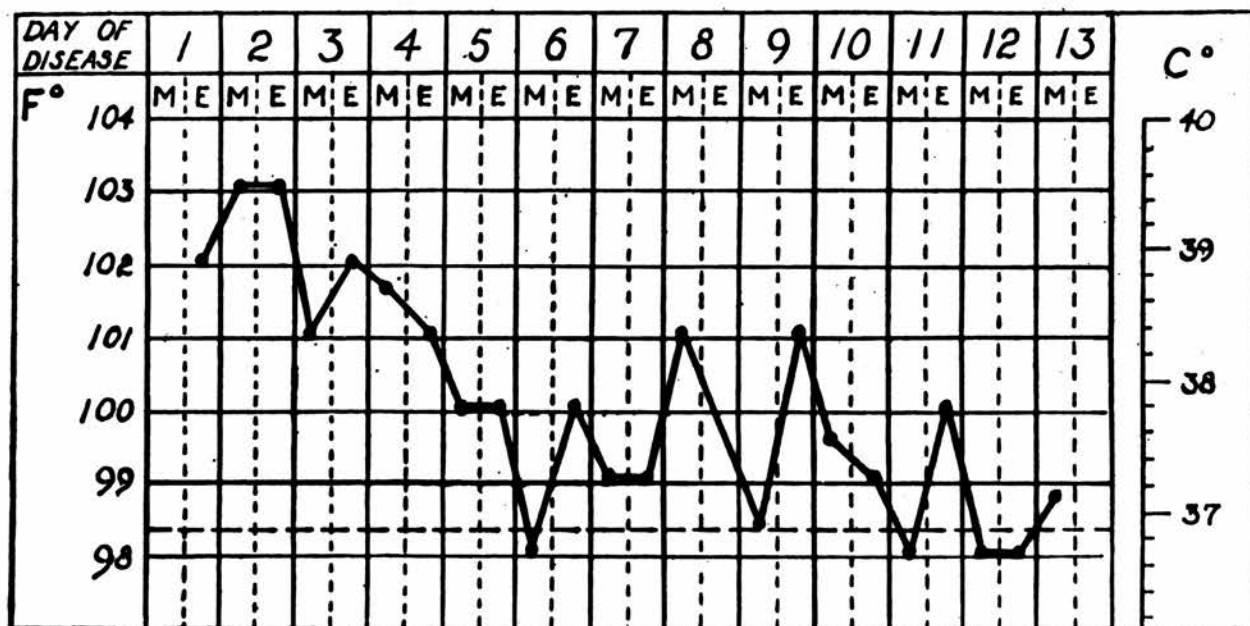


FIG. 13

Temperature charts of cases of leptospirosis not treated with antibiotics (after Trimble).



icterohaemorrhagica. (After Ryle.)

FIG. 14

Temperature chart of icterohaemorrhagica (after Ryle).

stiffness, diarrhoea, vomiting, abdominal discomfort and conjunctival suffusion. Meningitis has not been frequently reported in Malaya; neck stiffness so often recorded may be the result of muscle tenderness, and not of meningeal irritation, which may cause a false Kernig's sign and be responsible for an unnecessary lumbar puncture. In severe infections the critical lesion is almost always an acute lower nephron nephrosis similar to that sometimes found in crush injuries, burns or incompatible blood transfusions (Lancet 1960).

Trimble (1956) reports that leptospirosis in Malaya may be the cause of a three day fever, that it is commonly a moderately severe illness with pyrexia lasting a little over a week (Fig.13); but 3.4 per cent of his series of 236 cases were fatal and in 75 per cent the duration of the fever was 7-12 days. Fletcher (1928) in a review of 32 cases of leptospirosis reports that 25 per cent had fever lasting 7 days or less (Fig.15) while in all other cases it was of longer duration.

Secondary Fever:

Secondary fever may occur during the third week of the illness (Fig.16), when no chemotherapy is given, with recrudescence of symptoms. It is said that secondary fever cannot be called a relapse because no leptospirae are present in the blood during it, nor is the blood infective for guinea pigs; but immune bodies are present in the serum, and leptospirae can be found in the urine during the secondary fever (Fletcher 1928), yet secondary fever does not occur in cases treated with adequate doses of penicillin (Mackay-

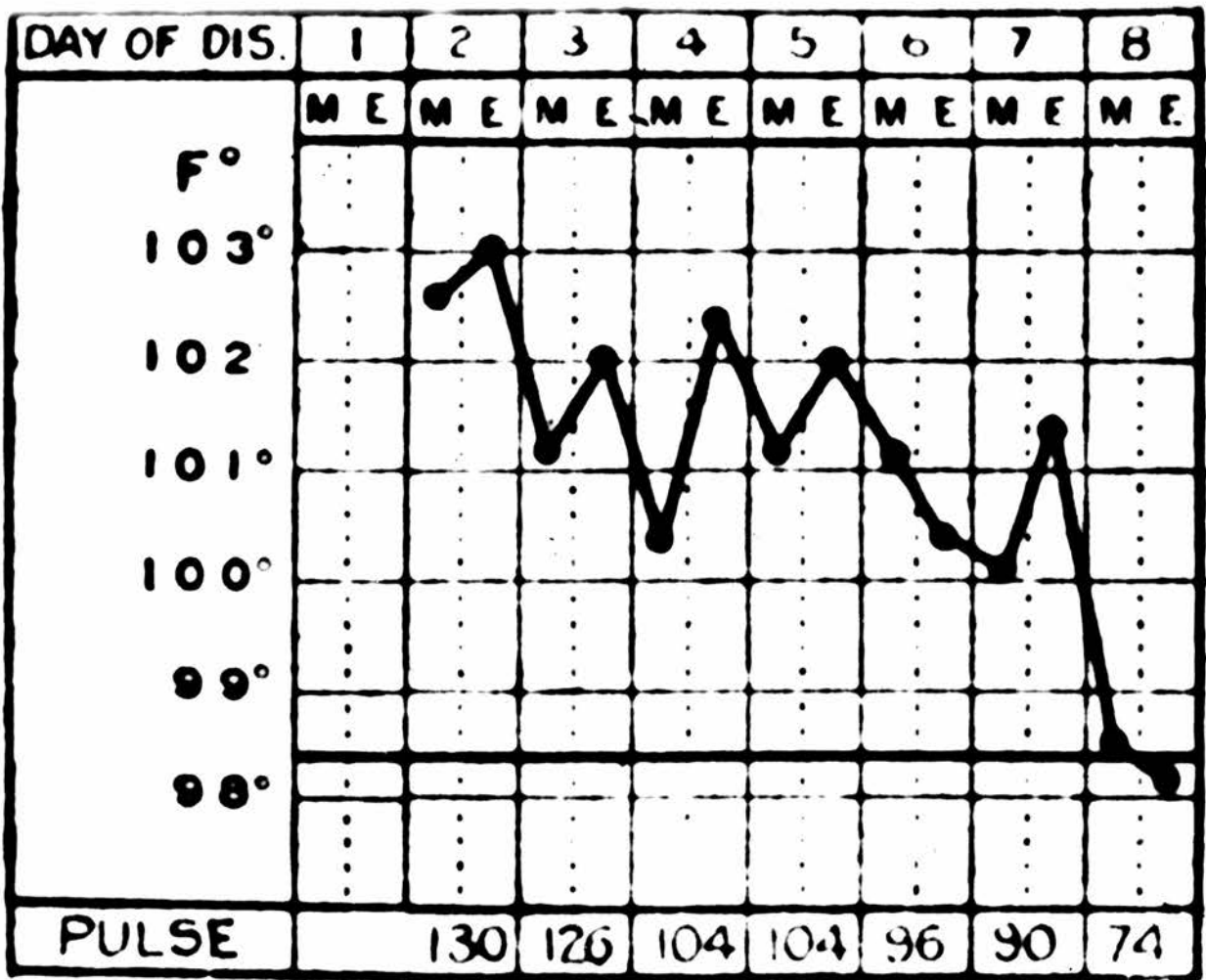


FIG. 15

The temperature chart of a patient whose fever lasted only seven days (after Fletcher), but pyrexia continued for more than seven days in threequarters of this series.

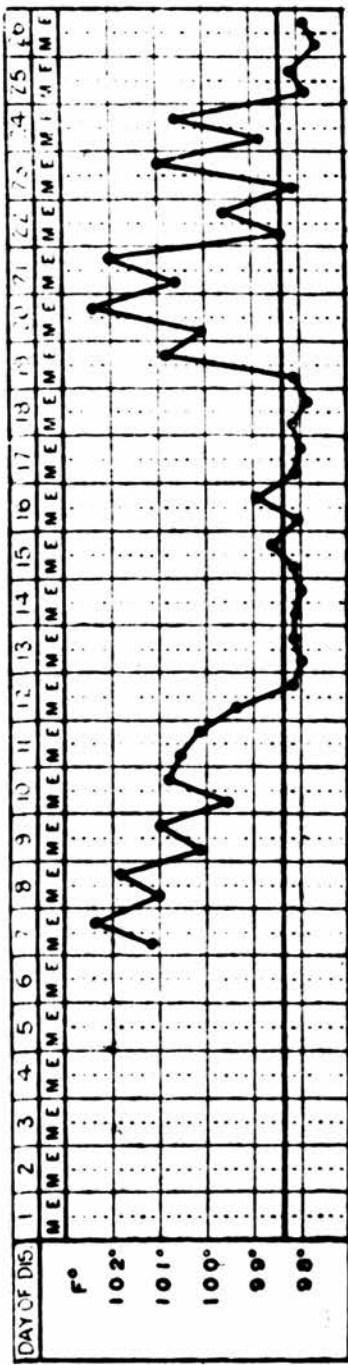


FIG. 16

The temperature chart of a patient who had an attack of secondary fever (after Fletcher).

Dick and Robinson 1957; Gsell 1966). In Hobson's (1952) experience secondary fever developed 4-19 days after the initial fever had subsided and persisted for varying periods of time (12-32 days). At this point it may be of interest to record that in British Military Hospital, Kinrara, Malaya all cases of short term PUO were sent for convalescence at a Hill Station, The Cameron Highland in Pahang; but never until the end of the third week following the onset of the illness. The reason for this was the all too frequent recurrence of fever during the third week with a recrudescence of symptoms. It was not good for our image that cases sent on convalescence should appear to become ill all over again. The duration of the secondary fever was around 36 hours. These cases had not received chemotherapy. We came to regard such secondary fever as almost being diagnostic of leptospirosis in retrospect as blood cultures were so often contaminated and the results of the agglutination reaction (AGR) took time.

In 19 cases of leptospirosis treated with penicillin Danaraj (1950) reported one case of secondary fever lasting 4 days, the intermediate afebrile period being 4 days. Trimble (1954) reported that 'secondary rises of temperature can occur after apparent settling and even definite relapses after some weeks of convalescence. Three of the latter have been reported from our hospital in the Cameron Highlands (Pahang) with return of all symptoms but so far only comparatively mild in severity'; but he also reports that 'a mild short secondary rise of temperature

(meaning secondary fever) is well known' as was also our experience (Mackay-Dick 1957). None of these cases had penicillin therapy. Lewthwaite (1928) reported secondary fever beginning 11 days after the termination of an initial fever of 9 days and lasting eight days.

In the first and second cases of leptospirosis recognised in Malaya a 'secondary rise' in temperature was noted as follows:-

- (a) Temperature of 98.2°F . on 6th day with a secondary rise on the 7th and 8th day, the temperature falling to normal on the 9th day.
- (b) Normal temperature on the 7th day with a secondary rise for the two following days as occurred with the first case.

(Fed. Malay States, Ann. Report Inst. Med. Research 1925).

Fletcher (1928) reported five cases of leptospirosis in which the patients had secondary fever which came on 5-11 days after the first attack was over and lasted for a period of 3-9 days. Dawson and Hume (1917) reported 100 per cent relapses in 14 severe cases and in 22 per cent in 58 mild cases. Davidson et al., (1934) reported 40 per cent relapses in 15 severe cases. According to Hobson (1952) the overall incidence of febrile relapses has been 28.0 per cent in the pre penicillin series as opposed to 10.6 per cent in the penicillin series. This difference he claims is statistically significant and suggests that penicillin diminishes the incidence of febrile relapses in leptospirosis. In our experience in Malaya with 140 consecutive laboratory proved cases of leptospirosis treated with penicillin there was no secondary

fever, variously referred to as relapses or febrile relapses (Mackay-Dick and Robinson 1959a). This is in line with the claims of Gsell (1966).

Hobson (1952) suggests that for the purposes of discussion a febrile relapse in leptospirosis is defined as a fever of 99 per cent or more which is maintained for four or more days and which develops four or more days after the initial fever has subsided. From my experience in cases of leptospirosis not treated with penicillin the duration of secondary fever was around 36 hours. The relatively wide variation in its duration may be due to infection with different serotypes.

Clearly 'secondary rise' in temperature (Fed. Malay States Ann. Report Inst. Med. Research 1925) - a not infrequent occurrence in febrile illnesses in my experience - and 'secondary fever' are not synonymous.

As it has never been established that secondary fever is due to a relapse of leptospirosis or to an immunity reaction, it is felt that it should be referred to as secondary fever; but it may be of significance that it does not occur in cases of leptospirosis treated long enough with adequate doses of penicillin no matter at what stage of the illness it is given (Mackay-Dick and Robinson 1957; Mackay-Dick and Robinson 1959a; Gsell 1966).

According to Turner (1967) the severity of leptospiral infection varies widely. At one end of the range are inapparent infections which may be subclinical or very mild, and be disregarded.



These may be detected by the presence of serum antibodies in persons with a known risk of infection but who deny any febrile illness.

Should such individuals develop another febrile illness then a negative blood culture and a low titre of antibodies should exclude a fresh attack of leptospirosis provided penicillin or terramycin or chloramphenicol have not been given before blood samples had been taken.

SUBCLINICAL CASES.Serological Survey of Troops Exposed to Infection with Leptospirosis
(Army Medical Department, Research Project 132 - Leptospirosis in Far
East Land Forces).

Bodies of troops moving into areas of presumed leptospiral activity were bled before and at intervals once, twice or three times after exposure, i.e. periods of duty lasting five months at a time on active service in the jungles of Eastern Malaysia (Sabah and Sarawak). The sera were examined in the Central Pathological Laboratory, Royal Army Medical Corps in Singapore, for leptospiral antibody by the haemolysin test. The number of sera tested on each occasion from each unit is given in Table 1. In parenthesis in each box is the number of positives found at each test. In the case of second, third or fourth bleeds, the number of positives given is not cumulative: that is, the figure in parenthesis is the number of new carriers of leptospiral antibody detected by the test concerned. However, serological testing is made difficult by the large number of serotypes of leptospire. The leptospiral agglutination test is the most specific, but it is not appropriate to large scale survey work as each serum must be tested against a number of separate pools of individual leptospires. Less specific tests have been devised, chiefly the complement fixation test, and the sensitised erythrocyte lysis or haemolysin (HL) test. These tests are suitable for survey work in the short term, as significant positive results are quite rapidly lost in convalescence. Because of the impossibility of

TABLE 1.

	1st Bn. *	2nd Bn.	3rd Bn.	4th Bn.	5th Bn.	6th Bn.	7th Bn.
FIRST BLEED	242 (6)	257 (33)	123 (26)	196 (22)	249 (36)	199 (25)	57 (6)
SECOND BLEED	159 (1)	230 (3)	119 (8)	169 (4)	229 (3)	161 (1)	57 (1)
THIRD BLEED	-	147 (4)	-	-	207 (1)	-	-
FOURTH BLEED	-	-	-	-	225 (11)	-	-

Serological survey of troops exposed to infection. Number bled on each occasion in each formation. New positive results found on testing in parenthesis.

N.B. Of the 191 individuals with positive results by the haemolysin (HL) test 154 arrived in the theatre (East Malaysia) already in possession of presumed leptospiral antibody. If the levels of antibody considered as significant of recent infection in this study are applied to these individuals, then the incidence of leptospirosis in the areas from which they came (W. Malaysia) must be as high or higher than in this theatre. A not unexpected finding. Nevertheless it is not known how many individuals had a short febrile illness designated as PUO or even ignored.

* Bn. = Battalion.

maintaining this large number of strains of leptospire in a routine laboratory, and for the reason given above, the haemolysin test was adopted as a screening procedure in this research. Work has been done in London which suggests that, using the haemolysin test, titres of 1:100 and below should not be regarded as significant. Accordingly the numbers of inapparent infections recognised shrink by half or two-thirds.

REVIEW OF 84 CASES OF LABORATORY PROVED LEPTOSPIROSIS
(Mackay-Dick and Robinson 1957) with Reference to 140 cases of
Laboratory Proved Leptospirosis all treated by Crystalline Penicillin
Parenterally (Mackay-Dick and Robinson 1959a and 1959b).

In this work we set out to establish the significance of territorial, residential and environmental history in the early diagnosis of leptospirosis: the recognition of the protean manifestations of this predominantly benign and anicteric disease so as to facilitate its early diagnosis and treatment: and the therapeutic effect of crystalline penicillin parenterally in adequate dosage given early enough, often enough and long enough. We came to recognise the clinical, therapeutic and diagnostic significance of a characteristic Herxheimer-like reaction in cases of leptospirosis when adequate penicillin therapy was begun during the septicaemic phase of leptospirosis; and from masterly inactivity in the management of this reaction, and the unfortunate experience of others, we avoided the use of vaso-constrictors to combat hypotension, the use of which could be lethal. We also noted that in all our penicillin treated cases there was no secondary fever or so called relapses and no late complications e.g. iritis (Mackay-Dick and Watts 1949). Clinical manifestations were as follows:-

Symptoms:

All cases complained of feverishness and 'flu'-like symptoms including headache (99 per cent), chills (78 per cent), generalised

TABLE 2.
COMMON SYMPTOMS IN LEPTOSPIROSIS.

Day diagnosis was made	No. of cases	Fever	Headache	Chills	Rigors	Generalised muscle pains	Abdominal pain	Vomiting	Cough
2nd	4	4	4	2	2	3	2	2	1
3rd	15	15	15	12	2	9	-	6	2
4th	25	25	25	22	2	13	4	6	5
5th	26	26	26	22	4	16	4	12	10
6th	14	14	13	8	3	10	1	4	6
TOTAL	84	84	83 (99%)	66 (78%)	13 (15%)	51 (60%)	11 (13%)	30 (35%)	24 (27%)

TABLE 3.

Day of disease	No. of cases	Conjunctival suffusion	Muscle tenderness	Tender right upper quadrant of abdomen	Liver palpable	Generalised lymphadenopathy	Signs in chest	Injection of throat	Neck stiffness	Herpes labialis
2nd	4	3	2	2	1	-	1	-	-	-
3rd	15	15	9	6	2	-	7	2	2	-
4th	25	25	13	11	4	1	11	1	3	1
5th	26	26	16	11	6	3	14	5	6	2
6th+	14	11	7	4	2	1	3	-	2	-
		95%	56%	40%	18%	43%	27%	9.5%	15%	3.5%

muscle pains (60 per cent), vomiting (35 per cent), cough (27 per cent), rigors (15 per cent), abdominal pain (13 per cent), severe diarrhoea (7 per cent). (Table 2).

It should be pointed out that diarrhoea occurred in three cases within 24 hours of commencing treatment with penicillin and in one case on the ninth day of the illness after five days of treatment. In no case were pathogens isolated from the stools.

Signs:

Conjunctival suffusion was present in 80 cases (95 per cent), muscle tenderness in 47 cases (56 per cent), generalised lymphadenopathy in 36 cases (43 per cent), tenderness in the upper right abdominal quadrant in 34 cases (40 per cent), adventitious signs in the chest in 23 cases (27 per cent), hepatomegaly in 15 cases (18 per cent), neck stiffness in 13 cases (15 per cent), splenomegaly in five cases (6 per cent) and herpes labialis in three cases (3.5 per cent). (Table 3). Towards the end of our series we noted oedema of the conjunctivae in many patients, but as this sign had not been noticed before we were unable to assess its frequency throughout the series.

We would like to stress three points in the diagnosis of leptospirosis, in the absence of jaundice and haemorrhage, shown by our series. None of our cases had the exquisite muscle tenderness reported by other observers; 95 per cent of our cases had obvious conjunctival suffusion, and rashes other than petechial haemorrhages were not noted in a single case. All cases felt and appeared ill and this was a striking feature when compared with other cases

admitted to hospital with pyrexia of unknown origin.

Haemorrhagic Phenomena:

In 17 cases (20 per cent) haemorrhages were present and in 10 of these they appeared shortly after penicillin therapy was begun. In seven cases haemoptysis occurred alone, in six haematemesis occurred alone, and in four haemoptysis and haematemesis occurred together. In one case of haematemesis there were associated bleeding per rectum, epistaxis and petechial haemorrhages into the skin. In one case of haemoptysis there was associated epistaxis. In this series, haemorrhages were not observed before the fourth day of the disease unless administration of penicillin had started.

Note: Before this series a patient with leptospirosis and epistaxis was treated with adrenaline nasal packs. Soon after their insertion he went rapidly downhill and died a cardiac death (Mackay-Dick and Robinson 1959a).

Jaundice:

Eighteen cases had jaundice (21.4 per cent). This appeared on the third day of the disease in two cases, on the fourth day in five cases, on the fifth day in seven cases and after the sixth day in four cases. It is interesting to note that jaundice became apparent shortly after the institution of penicillin therapy in several cases. Five cases with icterus had associated haemorrhages and these were seriously ill, the jaundice lasting 28 days. The remaining 13 cases ran a mild course and the average duration of

icterus was seven days.

Urinary Changes:

Of a total of 71 cases (84.5 per cent) which showed albuminuria or cylindruria while in hospital, 67 had urinary abnormalities on admission; 40 had albuminuria alone, whilst the remaining 27 showed cylindruria in addition. Four other cases developed albuminuria during their stay in hospital between the fifth and seventh day of illness.

There were five cases with anuria, which we defined as a condition when two ounces or less of urine are excreted in 24 hours. In two cases, admitted on the third and fourth day of the disease, anuria was present on admission. Of the remaining three cases, two were admitted on the fifth day and a third on the sixth day of the illness. All three became anuric following the commencement of penicillin therapy. The two cases admitted on the fifth day of the disease started penicillin within 24 and 48 hours of admission respectively, while the case admitted on the sixth day of the disease commenced penicillin three days after admission.

Four of the cases of anuria had associated jaundice and haemorrhage. No case developed polyuria of low specific gravity following the anuric phase, as is frequently observed in cases of anuria following infections for which no specific cure is available, e.g. epidemic haemorrhagic fever in Korea (Mackay-Dick et al., 1951). It is noteworthy that all cases of anuria showed low systolic blood pressure, but no cardiovascular stimulants were given as this might

have precipitated sudden death (Table 4).

Radiography of the Chest:

In every case a radiograph of the chest was taken on admission, and further films were taken if haemoptysis occurred or abnormal physical signs appeared in the chest. Thirteen per cent of all cases had abnormal chest radiographs of which three showed generally increased lung markings while eight showed bilateral mottling particularly at the bases. All cases in which mottling had been present during the acute stage had normal films after 10 days. In one case, showing mottled shadows, haemoptysis was absent, while three cases with haemoptysis had normal chest radiographs.

ECG Changes:

The occurrence of myocarditis has been reported in leptospirosis (Dragert 1934; Ashe, Pratt-Thomas and Kumpe 1941; Sutliff, Shepard and Dunham 1953), and for that reason, and because of past experience of collapse and death within hours in leptospirosis before this study, we decided to obtain ECG tracings in some cases. Bertucci (1945), referring only to Weil's disease due to *L. icterohaemorrhagiae*, stated that the electrocardiogram showed prolonged QT and PR intervals, defective AV conduction, functional or real incomplete AV blocks, low T waves, blocked auricular beats, sinus tachycardia and low voltage QRS complexes, these changes being reversible during convalescence. Other workers report evidence of myocarditis on post mortem examination.

TABLE 4.

CASES WITH ANURIA.

Average blood pressure during anuria	Day of disease at which onset of anuria	Duration	Specific Gravity of first urines after anuria
Systolic 80	3rd (j & h)	50 hrs	1016
Systolic 60-70	4th (j & h)	48 hrs	1018
Systolic 90	6th (j & h)	60 hrs	1020
Systolic 90	8th	24 hrs	1018
Systolic 60	9th (j & h)	48 hrs	1020

N.B. j & h - jaundice and haemorrhages.

Serial ECGs were performed on 10 of our cases. Four of these were selected on the grounds of clinical indications of myocardial disease, as shown by severe prolonged hypotension and irregularities of the pulse. The remaining six were consecutive admissions with uncomplicated leptospirosis of moderate severity. In all cases the first tracing was taken shortly after treatment with penicillin was started. A second tracing was taken during the stage of recovery, and in the case of abnormal results a third was obtained during convalescence.

The four patients with clinical signs of myocardial disease all showed ECG evidence of myocarditis and are described below.

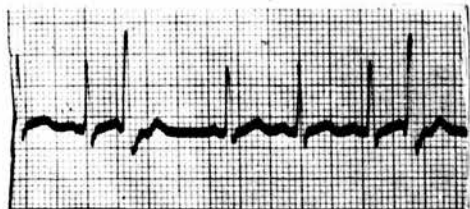
Case 1. Third day of disease. Gurkha soldier. Low voltage tracing with frequent ventricular extrasystoles and low T waves in leads I and II (Plate 1). By the twelfth day of disease the tracing had returned to normal (Plate 2).

Case 2. Fifth day of disease. Gurkha soldier. Low voltage tracing with widening of the QRS complex (0.14 secs) and low T waves in lead II and all V leads. By the seventh day of disease the tracing showed the T waves to be approaching normality and by the fourteenth day of disease the ECG was normal.

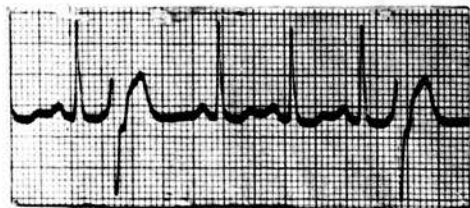
Case 3. Fifth day of disease. British soldier, aged 21. Low voltage tracing with low T waves in leads I and II. Normal by the fourteenth day of disease.

Case 4. Fourth day of disease. Gurkha soldier showed auricular

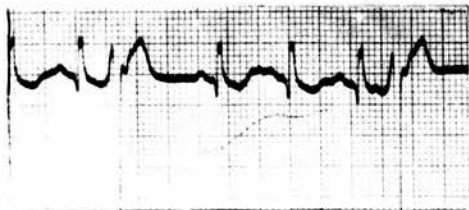
STANDARD E.C.G. LEADS OF CASE 1.



I



II

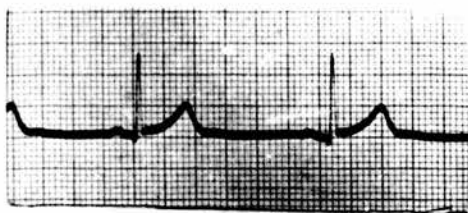


III

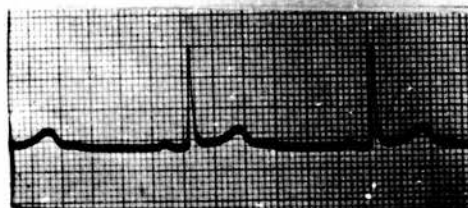
3rd day of disease showing
ventricular extrasystoles
tachycardia and low T
waves in I & II inverted
T wave in III, with a low
voltage tracing.

PLATE 1.

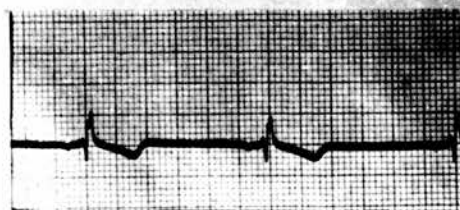
STANDARD E.C.G. LEADS OF CASE 1.



I



II



III

12th day of disease showing
almost complete reversion
to normal tracing.

fibrillation together with widening of the QRS complex and depressed T waves in all leads. Fibrillation lasted for eight hours and the ECG returned to normal by the tenth day of disease. This case had been provisionally diagnosed as bronchitis with severe bronchospasm by his medical officer who treated him with penicillin, resulting in the characteristic Herxheimer-like reaction, and ephedrine which may or may not have precipitated the auricular fibrillation confirmed by ECG. On admission to hospital penicillin was continued with excellent results. Ephedrine was discontinued and in a matter of hours auricular fibrillation was no longer present (Mackay-Dick and Robinson 1959a).

Of the six consecutive uncomplicated cases, two showed minor irregularities of the QRST complex on the fifth day of the disease, which returned to normal by the seventh day. The remaining four cases showed no ECG changes other than sinus tachycardia.

Parsons (1965) suggests that the underlying pathology in cases with clinical signs of myocarditis could well be spontaneous bleeding in the myocardium or pericardium, while ECG changes in cases of leptospirosis without clinical evidence of cardiovascular disease are the non-specific result of a febrile illness.

Blood Count:

In all cases there was a relative or absolute polymorphonuclear leucocytosis with a total white cell count varying from 4100/c.mm. to 20,300/c.mm. The average white cell count was between

8000/c.mm. and 9000/c.mm.

Cerebrospinal Fluid:

Lumbar puncture was performed on three occasions and the cerebrospinal fluids found to be normal. Neck stiffness in 15 per cent of cases was probably due to muscle tenderness and therefore misleading as regards possible meningitis.

Severity of Cases:

The illness was considered to be severe when serious complications such as multiple haemorrhages, severe myocarditis and severe jaundice or anuria occurred (Table 5).

TABLE 5 - CASES CLASSIFIED ACCORDING TO SEVERITY.

Day of disease on which treatment started	Number of cases	Severity of illness	
		Mild	Severe
2nd	4	3	1
3rd	15	11	4
4th	25	22	3
5th	26	25	1
6th +	14	10	4

RESULTS OF SPECIAL INVESTIGATIONS.Blood Culture:

Blood culture was positive in 29 per cent of cases, of which six were taken on the third day, eight on the fourth day, nine on the fifth day and one after the sixth day of the illness.

Complement Fixation Test (CFT).

We are unable to assess accurately the results of the complement fixation test (CFT) as towards the end of this series the antigen used gave inconsistent results. The high incidence of 'negative' blood cultures was due essentially to contamination.

Agglutination Reaction (AGR).

In 39 per cent of cases the agglutination reaction (AGR) alone was positive, while in 25 per cent of cases the CFT and AGR were positive in the absence of a positive blood culture. In six cases the CFT was the only positive finding when the second specimen of serum for the AGR was damaged in transit. Only in one case was the CFT positive when both blood culture and AGR were negative. The presence of a positive CFT makes the diagnosis certain, but on occasion this test may be negative when other tests are positive (Table 6).

**TABLE 6 - RESULTS OF BLOOD CULTURE, COMPLEMENT FIXATION
TEST (CFT) AND AGGLUTINATION REACTION (AGR).**

No. of cases	Blood culture	CFT	AGR
12	Positive	Positive	Positive
6	Positive	Negative	Positive
5	Positive	Negative	Not done*
1	Positive	Positive	Not done*
32	Negative	Negative	Positive
21	Negative	Positive	Positive
6	Negative	Positive	Not done*
1	Negative	Positive	Negative

* The AGR was not performed in these cases as the bottle containing the second specimen was broken in transit.

It should be mentioned that in several cases out of a series of 140 consecutive laboratory confirmed cases of leptospirosis where the blood culture was positive the AGR titre in the second specimen was not diagnostic. Broom (1956 - personal communication) agreed that these must be regarded as true cases of leptospirosis in which the production of antibodies is unusually slow, and possibly the early administration of penicillin may explain this phenomenon. Gsell (1966) and Turner (1969) hold similar views.

Repeated Attacks:

One soldier, after an interval of months, had a second attack of leptospirosis due to a different species from the first. Both attacks responded dramatically to penicillin. Broom 1956 (personal communication) from the results of his laboratory tests, 'concluded that one can be reasonably sure that this is a second attack due to a different species from the first.' In this case a previous infection had not conferred absolute immunity, if any. Trimble (1956) reported two cases of proved second attacks.

Concurrent Infection with Two Serotypes:

In another case with a positive blood culture Broom, from his serological tests, concluded that culture reacted to a titre with anti-sera from both *bataviae* and *L. medanensis*, both being quite unrelated antigenically. Broom 1956 (personal communication) expressed the opinion that the possibility of a concurrent infection with the two serotypes must be considered.

Outline of Treatment (Mackay-Dick and Robinson 1957):

The aim of treatment was to maintain adequate hydration and electrolyte balance, to relieve headache and pain with pethidine and to commence penicillin therapy as soon as possible, namely, well within the septicaemic phase of this disease. This was combined with careful nursing, optimum position in cases with hypotension on penicillin therapy and the avoidance of vasoconstrictors e.g. nor-adrenaline drip which we believe are dangerous in such circumstances.

It was calculated that obviously dehydrated patients required 6 per cent of their body-weight as fluid replacement. Half of this fluid was given by continuous intravenous drip as normal saline and half as 5 per cent dextrose in water in the absence of renal impairment. In the presence of vomiting, equivalent volume of normal saline was given by intravenous infusion. The average daily basic requirement was assessed as three litres of fluid in 24 hours, one-sixth of this was given as normal saline and five-sixths as 5 per cent dextrose in water. Where the patient had oliguria due to impaired renal function the regime was modified accordingly.

The initial dose of crystalline penicillin was 600,000 units given intramuscularly, and this dose was repeated four-hourly for 24 hours and then six-hourly until the seven days therapy had been completed.

All five cases of anuria were managed with a regime first described by Bull, Koekes and Lowe (1949) and did well. Three patients who developed anuria before this series was started would not tolerate this regime. In these, however, we restored a reasonable state of hydration and electrolyte balance intravenously. We gave two pints of 40 per cent glucose in water by continuous infusion through polythene tubing into the inferior vena cava. All three patients survived although two had been dangerously ill and had haemorrhagic manifestations and deep jaundice.

Effects of Penicillin Therapy (Mackay-Dick and Robinson 1957):

When penicillin was given before the sixth day of the illness, that is to say on or before day 5, the duration of the fever was reduced from an average of about 34 hours to one of about 18 hours (Table 7). At the same time symptoms were ameliorated. However, when penicillin was given on or after day 6 of the illness, no reduction in the period of pyrexia was observed, although in individual cases the symptoms were relieved and the fever fell more rapidly than in untreated cases. Furthermore, irrespective of what day of the illness penicillin therapy was begun, secondary fever never occurred.

A significant proportion of patients suffering from leptospirosis develop a characteristic Herxheimer-like reaction following the administration of penicillin (Plates 3 and 4) provided it is given early enough (Mackay-Dick and Robinson 1957; Turner 1967 and 1969). The nature of this reaction would appear to be one of sudden increase of toxæmia. Penicillin is leptospira-chaeticidal (Garrod 1959). Therefore when penicillin is given in the septicaemic stage of this disease it is suggested that there is massive destruction of leptospirae with liberation of much endotoxin. Such was the frequency of this reaction that I designated it the diagnostic penicillin-leptospiral response (Mackay-Dick and Robinson 1957). Reactions of this type, followed by rapid relief of symptoms, have been described by some workers (Covaleda et al., 1953; Crooks and Blair 1955) but not by others. A leading article in the British

TABLE 7.

TIMING AND EFFECT OF PENICILLIN TREATMENT.
(MacKay-Dick and Robinson 1957).

Day of disease when penicillin first given	No. of cases	Duration of pyrexia after start of treatment (hours)	
		Range	Average
2nd	4	12 - 30	20
3rd	15	8 - 30	16
4th	25	5 - 30	17
5th	26	10 - 30	18
6th +	14	14 - 60	34

RESPONSE TO PENICILLIN IN A GUERRA SOLDIER AGED 23
SUFFERING FROM LETHARGIC TYPHOID

February 1956

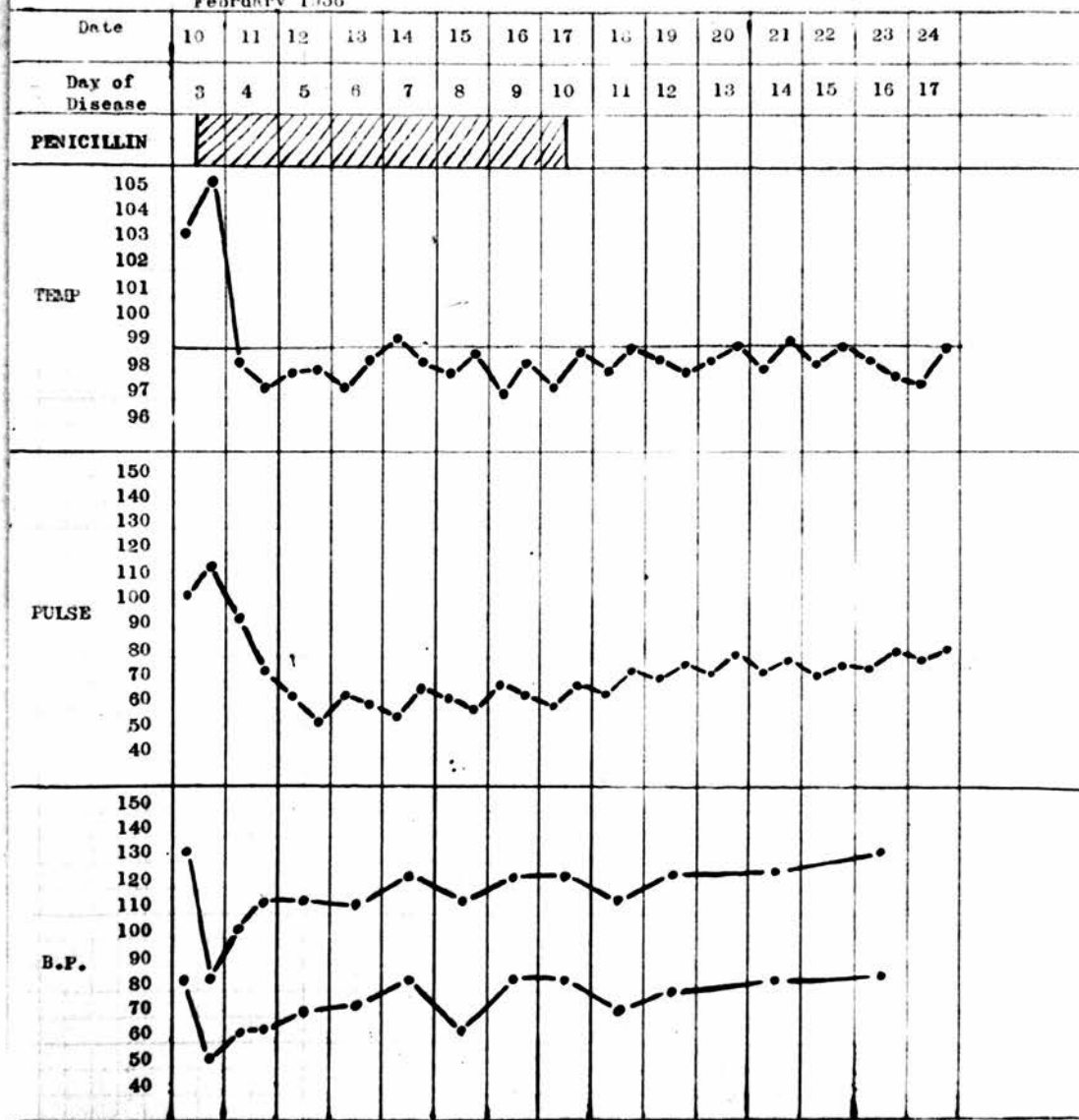


PLATE 3.

Daily chart showing characteristic response to early and adequate penicillin therapy.

2 HOURLY CHART SHOWING REACTION TO TREATMENT WITH PENICILLIN

3rd DAY OF DISEASE

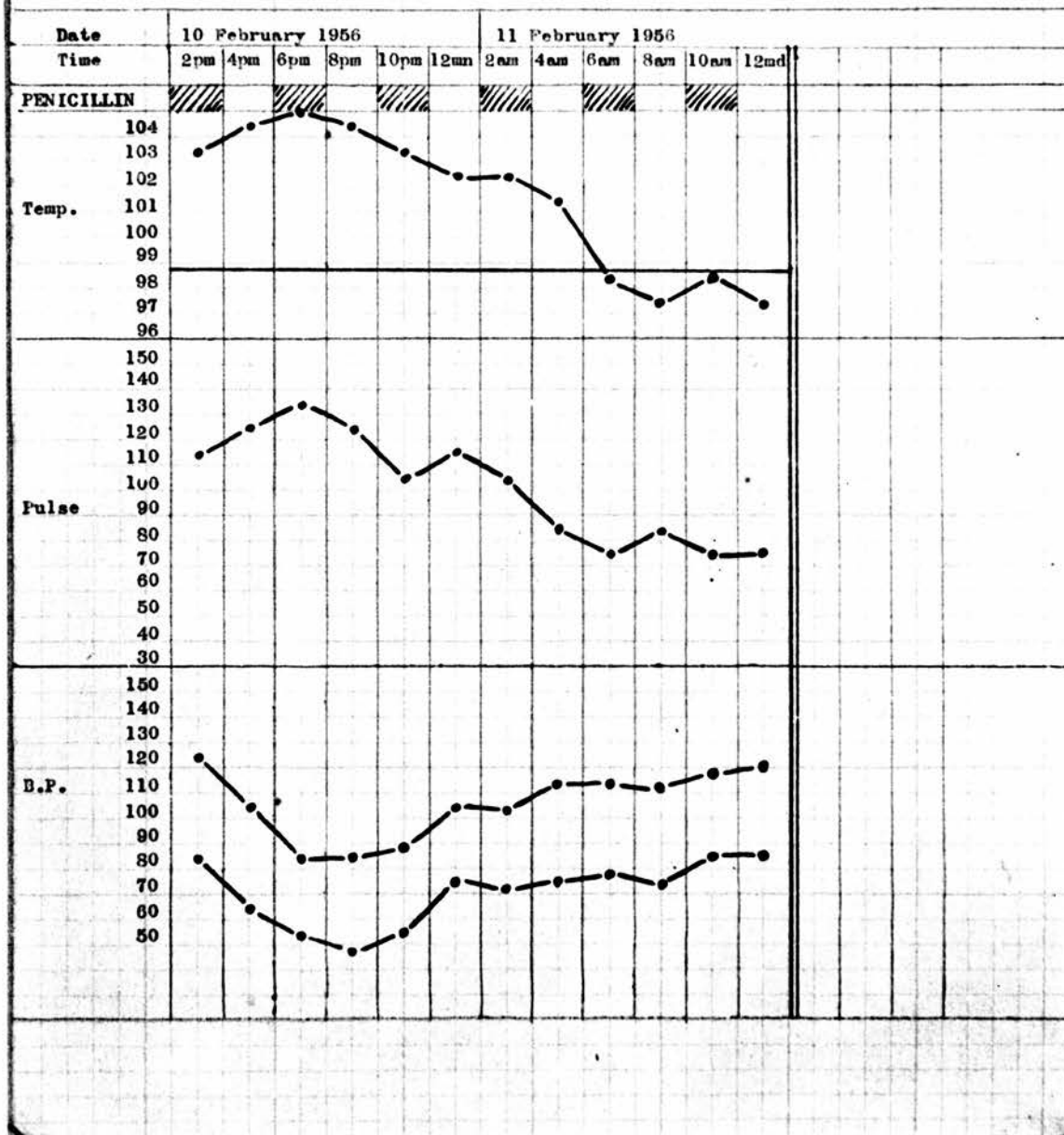


PLATE 4.

2-hourly chart showing characteristic response to early and adequate penicillin therapy. Note the effect on the temperature, pulse rate and blood pressure

Medical Journal (1958) states that it is improbable that so many in the Malayan series (Mackay-Dick and Robinson 1957) could be sensitive to penicillin so the authors' suggestion seems the most likely explanation of the reaction. All these cases were treated in a military hospital with general medical, surgical and dermatological beds for security forces, as well as beds for service dependants, including obstetrical and gynaecological beds and a large children's ward where penicillin was in everyday use; and as this Herxheimer-like reaction, which in no respect mimics hypersensitivity reactions to penicillin per se, was seen only in cases of leptospirosis diagnosed and treated early, it was felt that our explanation regarding the cause of the reaction was the only acceptable one in the circumstances; particularly as the pattern of response to adequate penicillin therapy given early enough is found consistently (Cook 1959) and in all we treated 140 cases of laboratory proved cases of leptospirosis before I left Malaya in March, 1958 (Mackay-Dick and Robinson 1959a); and the absence of secondary fever in all these penicillin treated cases accords with the experience of Gsell (1966).

At this point it should be stressed that out of 90 cases provisionally diagnosed as leptospirosis, 84 (93 per cent) were proved in the laboratory (Mackay-Dick and Robinson 1957). Although we should be content with this high diagnostic rate, we noted that several of the six remaining cases showed the characteristic response found in cases of leptospirosis treated early with adequate penicillin (Mackay-Dick and Robinson 1957). I was convinced that the provisional diagnosis of leptospirosis was correct in spite of the

fact that blood culture, complement fixation test and agglutination reaction were all reported as negative. As already stated Gsell (1966) has shown that in cases treated early with adequate antibiotic peak titres are likely to remain low not warranting a laboratory diagnosis of leptospirosis; and in some cases there may not even be detectable antibodies during the ensuing weeks.

Penicillin-Leptospiral Response (Mackay-Dick and Robinson 1957):

The reaction is characterised by an increase in severity of symptoms already present, an acceleration of appearance of symptoms, an increase in - and fresh development of - physical signs, a brisk rise in temperature, amounting to a rigor in one-fifth of these cases, and a fall in blood pressure. It occurs typically 4-6 hours after the first dose of crystalline penicillin (6000,000 units stat repeated four hourly for 24 hours and continued six hourly to complete seven days). This penicillin-leptospiral reaction occurred in 83 per cent of all cases and in 88 per cent of cases treated on or before day 5 of the illness. Its duration on an average is 18 hours. Fifty nine (84 per cent) had a sharp rise in temperature and 58 (83 per cent) a severe fall in blood pressure. In addition, in 31 cases (44 per cent) there was a precipitation or aggravation of classical symptoms and signs of leptospirosis. As regards haemorrhagic phenomena these may appear at any stage of the disease; but in our series their usual time of occurrence was within 12 hours of the initial dose of penicillin. In no case did haemorrhages appear for the first time after 12 hours of penicillin. This gave rise to the

opinion that if haemorrhages are going to occur they are precipitated by penicillin therapy. All 70 (83 per cent of all cases) treated within five days of the estimated date of onset of the illness shared in this elevation of pyrexia and fall of blood pressure in some measure. The reaction was mild to moderately severe in 60 (86 per cent of all affected cases) and severe in 10 (14 per cent).

Some alarm was caused by the apparent collapse and appearances of these patients, but penicillin therapy was continued and no additional treatment prescribed. Within 24 hours the patients had completely recovered from their reaction, the duration of which approximately equalled that of the pyrexia following the commencement of penicillin therapy. We came to regard this reaction as an indication of a good response to treatment and as a useful diagnostic sign in leptospirosis, and soon it was named the 'Diagnostic Penicillin-Leptospiral Response'.

We noted that during the hours immediately following the onset of the reaction, a high specific gravity oliguria occurred in all cases except in the three who became anuric. Once the blood pressure returned to normal, the urinary output did likewise without the passage of persistently low specific gravity urine.

The average duration of hypotension was 24 hours, although in cases in which penicillin therapy was started after the fifth day of the illness, the blood pressure was rather low before treatment (averaging 110/70) and slowly returned to normal within seven days (Tables 8 and 9).

TABLE 8.
PENICILLIN-LEPTOSPIRAL RESPONSE (PLR).

Day of disease on which Treatment was begun	Total No. of cases	No. of cases showing a PLR	Percentage showing PLR	Severity of PLR	
				Mild	Severe
2nd	4	4	100	3	1
3rd	15	13	86	8	5
4th	25	22	88	19	3
5th	26	23	88	23	-
6th +	14	8	57	7	1

TABLE 9.

NATURE OF PLR.

No. of cases with sharp rise in temperature	Average rise of temperature	Fall of blood pressure	Average fall of blood pressure (systolic)	No of cases in which symptoms/signs precipitated/aggravated by penicillin
3	105° F.	3	90/60mm. of Hg.	3
11	105° F.	13	90/60mm. of Hg.	10
16	104° F.	20	80/50mm. of Hg.	8
22	104° F.	17	80/50mm. of Hg.	4
7	103° F.	5	80/50mm. of Hg.	6

The first two columns in Table 8 should be read in conjunction with Table 9.

Our findings indicate that penicillin given on or before day 5 of the illness has a definite therapeutic value. We also believe that penicillin should be given no matter on what day of the disease the patient comes under medical care. The dramatic response of the illness seen in patients treated earlier with penicillin is absent in these late cases but in all cases secondary fever does not occur; in addition penicillin may also prevent any prolonged impairment of renal concentrating power, and late complications have not been reported.

This pattern of response to penicillin therapy was characteristic in 140 consecutive laboratory proved cases of leptospirosis treated under my direction before I left Malaya in 1958 (Mackay-Dick and Robinson 1959a).

Even now some medical officers are rather apprehensive of the severe cases of penicillin-leptospirosis response but no harm will normally come to the patients if, in my opinion, they are left alone and receive no form of treatment other than the continuation of penicillin therapy, appropriate fluids and nutritive measures. To my knowledge fatalities in such cases arise where special measures are taken with the intention of combating the severe signs and symptoms of this reaction e.g. the giving of vasoconstrictors or the administration of a nor-adrenaline drip. Furthermore during the period of hypotension care must be taken over the administration of fluids intravenously for fear of precipitating cardiac failure. In such circumstances we found that to raise the foot of the bed was an added danger to the life of the patient (Mackay-Dick and Robinson 1959a).

It is well known that there is a fall in blood pressure when fever subsides by crises in many diseases. However, in these cases the fall in blood pressure occurred whilst there was a high temperature.

Interrupted Treatment and Second PLR:

At this point I would mention that Robinson (1957), on temporary duty in another hospital in Malaya, ordered penicillin in the early evening in a suspected case of leptospirosis. The patient had a brisk penicillin-leptospiroal reaction at the usual time. The night sister at once summoned the orderly medical officer who stopped penicillin administration believing that the patient was hypersensitive to it. The following morning Robinson, on learning that penicillin therapy had been stopped, restarted the penicillin and the patient had another brisk penicillin-leptospiroal reaction but penicillin therapy was continued, without anything further untoward happening.

It has been suggested to me that at the commencement of treatment of leptospirosis the administration of intravenous hydrocortisone in conjunction with penicillin for the following 24 hours may suppress some of the features of the penicillin-leptospiroal reaction without necessarily depriving it of its diagnostic value. Suggested doses of intravenous hydrocortisone are 200 or 300 mg. with the first dose of penicillin and then 100 to 200 mg. every three hours or so for the next 24 hours (Gonzalez 1964 - personal communication). These patients do not suffer from absolute adrenal insufficiency but 'may suffer from a relative insufficiency because of the intensity of

the toxæmia' (Morrison 1966 - personal communication). The hydrocortisone, I am informed, is used for its pharmacological action on the micro circulation preventing the profound vasoconstriction with all its consequences. To be effective it has to be given in big doses of 1 to 2 g. in 24 hours and then discontinued without tailing off (Gonzalez 1964 - personal communication). McKelvey (1964) in a personal communication said that he had been using intravenous hydrocortisone in certain cases and had not found it to be completely successful in preventing the hypotension consequent upon penicillin. He suggested that he might have used larger doses of hydrocortisone.

Using intravenous tetracyclines in suspected, and later established, leptospiral illness in 1955, alarming Herxheimer-like reactions occurred but their true significance was not appreciated at the time (Mackay-Dick and Robinson 1959a). The nursing staff were relieved when intravenous tetracyclines ceased to be used as they felt that the treatment was worse than the disease - an opinion echoed by at least one doctor who still refuses to use penicillin in leptospiral illness because of the alarming nature of the penicillin-leptospiral response.

VIEWS ON VALUE OF PENICILLIN THERAPY IN LEPTOSPIROSIS.

Conflicting reports have been expressed regarding the therapeutic value of penicillin in leptospirosis. Favourable reports included those from Hart (1944), Carragher (1945), Bulmer (1945), Cross (1945), Baber and Stuart (1946), Niems (1946), Paterson (1947), Moreau et al., (1947), Smith (1949), Danaraj (1950), Lawson (1951), Varfolomeeva (1951), Suchett-Kaye (1951), Doherty (1955 and 1960), Clein (1956), Mackay-Dick and Robinson (1957; 1959a; 1959b), Cook (1959), Critchley (1962), Turner (1967 and 1969) and Gsell (1966): while Broom (1953) noted that physicians very often recorded clinical improvement after the administration of penicillin. From these reports it was noted that when the time of commencement of penicillin therapy, and the dosage was comparable, the results on the whole corresponded with Doherty (1955). On the other hand Fairburn and Semple (1956) treated 21 cases of leptospirosis with 2,400,000 units of penicillin daily and concluded that penicillin was of no value in that disease.

Broom (1951) reported that the death rate among 152 jaundiced cases of true Weil's disease treated with penicillin in various hospitals in England during 1947 - 1950 was 22 per cent compared with 23 per cent of 103 jaundiced cases which did not receive the drug. A series of 67 patients in Puerto Rico, about half of whom were infected by icterohaemorrhagiae, were treated with various antibiotics, including penicillin, by Hall et al., (1951); when the results were

compared with those from a control group of 12 who received no antibiotics, the conclusion was reached that none of the antibiotics was effective.

Hobson (1952) concluded that penicillin does not influence the duration of fever of cases but diminishes the incidence of febrile relapses. Hall et al., (1951) concluded that no antibiotics were effective treatment in leptospirosis.

According to Garrod (1959) 'conclusions on therapy are pessimistic. There is no good evidence of benefit from penicillin or other antibiotics given at a time when a diagnosis is usually made. No attempt is made to reconcile this finding with the high susceptibility of the organisms in vitro - a discrepancy for which there must be some explanation.' It is suggested that the answer to that question is that penicillin was being given later than believed and therefore at a stage of the illness when penicillin does not, and could not, be expected to provide striking results (Mackay-Dick and Robinson 1959b). After all, initially the infection is predominantly a septicaemia, when antibodies are few, and so leptospirae at this stage are expected to be acutely vulnerable to a leptospirochaeticidal antibiotic such as penicillin. On destroying the leptospirae endotoxin is liberated, resulting in a Herxheimer-like reaction with precipitation and aggravation of the manifestations of leptospirosis.

In cases not treated by antibiotics there is in the first few days of the illness insufficient toxin in the tissues, especially the myocardium, liver and kidneys to produce significant tissue damage.

After the first week in such cases not treated by appropriate antibiotics it is suggested that the leptospirae will be destroyed by the patient's own antibodies, but the concentrations of toxins in the tissues will be greater then, because of the greater number of leptospirae, and so greater damage results in these tissues. By the time this has happened neither antibiotics nor antitoxins can be expected to be of particular value (Mackay-Dick and Robinson 1959a and 1959b) except perhaps in the prevention of secondary fever (Mackay-Dick and Robinson 1957) or in lessening its incidence (Hobson 1952) as well as in the prevention of late complications.

The current view is that large doses of penicillin given early in the course of a suspected leptospiral illness are indeed advantageous (Turner 1969). Gsell (1966) has emphasised the correlation between the duration of the illness and the effects of effective antibiotic treatment. He recommends 2.4 mega units per day if treatment before day 4 of illness; but that the initial dose should be 6-10 mega units if treatment on day 4 or later; and in each case the succeeding doses should be 2.4 mega units per day for a further six days. Our regime (Mackay-Dick and Robinson 1957) also extends over seven days with 3.6 mega units on day 1 (600,000 units 4 hourly) and 2.4 mega units daily thereafter (600,000 units 6 hourly).

For reasons already stated we have yet to understand how massive doses of penicillin initially in cases treated later than the sixth day of the illness, may have any advantage, early or remote,

over cases treated with the doses used by Mackay-Dick and Robinson 1957 (Mackay-Dick and Robinson 1959a). Cook (1959) confirms the pattern of response to penicillin irrespective of serotype. In our experience impairment of hepatic and renal function is dealt with conventionally, the latter in these modern days being treated by renal dialysis. Nevertheless we managed very well with the conservative Bull regime when we did not have 'the artificial kidney' available (Mackay-Dick and Robinson 1957). However, all our cases from East Malaysia in 1966 with severe renal failure were evacuated by air to Singapore for treatment with the artificial kidney and there were no fatal cases. There is also evidence that renal function is not permanently impaired (Simpson et al. 1967). Gsell (1966) recommends giving prednisone 20-40 mg. with laevulose in an intravenous drip + 30 mg. orally for jaundice. Gsell (1966) also recommends massive doses of penicillin in debilitated subjects. We have no experience in the treatment of such cases but in view of our results with penicillin we cannot envisage any advantage in using massive doses. These latter might aggravate the severity of the penicillin-leptospirosis response and in any case it might be wise to use prednisone routinely as a cover for the first 24 hours of penicillin therapy in debilitated patients.

All types of leptospirae are sensitive to penicillin; but to be effective in experimental infection such treatment had to be started during the incubation period (Alston and Broom 1944). Prophylactic administration of penicillin failed in a case of

laboratory infection in which six million units of penicillin were given orally over three days starting one hour after infection (Broom and Norris 1957); but surely that does not dissuade us from advocating appropriate antibiotic therapy in cases of special exposure to leptospirosis. When a laboratory worker is known to have been contaminated with a virulent strain, or with a recently isolated one, or when an animal handler has contact with material from an infected animal Turner (1969) recommends that a course of penicillin should be started at once. This is what I recommended in Sabah and Sarawak during the Indonesian Confrontation in respect of circumstances of special exposure of patrols on active service. These special circumstances already detailed were 'river crossing, river in spate, dropped weapon(s) with prolonged and repeated diving to retrieve same'. This recommendation could also apply to repeated and prolonged diving to recover a body but in these conditions the divers would doubtless wear special suits and equipment so exposure risk would be significantly lessened. In this connection the following true story may be of interest. Around one-third of a patrol of an infantry battalion on return to Western Malaysia from duty in the jungles of Sarawak fell ill with leptospirosis. Just prior to leaving Sarawak the patrol had dived in relays in a river in spate to retrieve a dropped weapon. During this battalion's next stint in East Malaysia (Sabah) a young officer, who had been on that patrol and had been one of those to acquire leptospirosis, was in charge of a patrol crossing a river in spate. A Malaysian sapper, attached to the battalion, and who was

a powerful swimmer, uttered a cry in mid-stream and sank like a stone not to reappear. All ranks took it in turn to dive repeatedly in relays to recover the body but without success. In the light of his previous experience of a high incidence of leptospirosis in a patrol following repeated diving to retrieve a weapon dropped in a river in spate, he instructed the patrol to take oral terramycin according to the routine in all cases of gunshot wounds namely, 500 mg. stat and 250 mg. 6 hourly. This could not be regarded as a controlled trial but coincidentally or otherwise no members of the patrol on this occasion developed leptospirosis. On return to the United Kingdom I was interested to hear the senior partner of a group practice in a predominantly agricultural county of England say that it was his practice to prescribe oral terramycin in all cases of rat bite. It is accepted that rats, infected with leptospirosis, by licking their genitals, may spread this disease by their bite; but like mice they may infect the bitten area by urinating on it at the same time.

POINTS FOR NOT HAVING A CONTROLLED TRIAL IN OUR SERIES
OF 140 LABORATORY PROVED CASES OF LEPTOSPIROSIS.

We were criticised for not having a controlled trial in assessing the efficacy of penicillin in the treatment of leptospirosis (Semple 1959). As we have pointed out a detailed knowledge of the natural course of the infection in humans would be of great value in assessing the efficacy of any therapeutic agent; and we know that initially leptospirosis is a septicaemia and penicillin is leptospirochaeticidal. What is therefore of significance in the assessment of the therapeutic value of penicillin is not only the size and frequency of the dosage but the day of the disease on which therapy was instituted (Mackay-Dick and Robinson 1957). We suggest that the reason that some workers have reported disappointing results from penicillin therapy in leptospirosis is insufficient significance has been attached to these points (Mackay-Dick and Robinson 1957 and 1959b).

Our reasons for not having a controlled trial were as follows:-

- (a) Many individual cases and small series of the infection have been reported, and when the time of commencement of penicillin therapy and the dosage were comparable the results on the whole have corresponded with those of Doherty (1955 and 1960) and since supported, among others, by Gsell (1966) and Turner (1967; 1969).
- (b) The results of our treatment of our first dozen cases of

leptospirosis, with penicillin were so dramatic and so convincing that our conscience would not allow us to deprive our jungle fighters of penicillin. It has been said that there are circumstances when a controlled trial is not mandatory and we felt that this was one of them.

- (c) Our decision not to have a controlled trial was therefore deliberately taken. Much of the work on the diagnosis, clinical manifestations and methods of treatment reported after World War II from Malaya (now Western Malaysia) was carried out on security forces in British Military Hospitals (Hobson 1952; Trimble 1956; Fairburn and Semple 1956; McCrumb et al., 1957 and Russell 1958) while the annual reports of the successive consultant physicians, Far East Land Forces, were a mine of information (Hughes 1954; Trimble 1955). Accordingly, as so much work had been done in the previous five years on security forces in Malaya (1950-55), from the same leptospiral environments that we were to draw our cases, we felt that the patients studied by our predecessors could act as phantom controls (Mackay-Dick and Robinson 1959a).
- (d) In the diagnosis of leptospirosis the identity of the particular serotype is determined reliably only by isolating it and identifying it (Turner 1969) and that takes time making a controlled trial with balanced serotype for serotype well nigh impossible (Mackay-Dick and Robinson 1959b) except in retrospect. That was one of our objections to the validity of the controlled

trial by Fairburn and Semple (1956). Another was that provided the penicillin used by Fairburn and Semple was not of reduced potency the only conclusions that we could draw, in view of our results with early penicillin therapy, and that of others, was that their cases had been treated later than they thought (Mackay-Dick and Robinson 1959b).

Medical officers in Eastern and Western Malaysia, who have witnessed the characteristic Herxheimer-like reaction following adequate penicillin early in the septicaemic phase of leptospirosis, have expressed astonishment that more attention had not been drawn to it before. Perhaps it was ignored because it was erroneously regarded as a hypersensitivity reaction to penicillin which it most certainly is not. Those of us who learned our clinical medicine in the pre-sulphonamide era, and who have had much experience of febrile disease in the tropics and sub-tropics, were most punctilious in estimating the day of the illness on admission of the patient to hospital. In our clinical assessment of febrile patients this was a special aid in clinical diagnosis and of course in determining laboratory investigations as well as interpreting the results (Mackay-Dick and Robinson 1959b). According to Doherty (1960) - 'Clinical experience in North Queensland, supported by analysis of 264 cases (Doherty 1955) is in complete agreement with the opinions of Mackay-Dick (1957) and Cook (1959). The practitioners in the area when approached in 1953, considered that it was not justifiable to withhold treatment (with penicillin) from patients. It was not, and

will not be, possible therefore to attempt a controlled trial.'

These were also our views (Mackay-Dick and Robinson 1959a; 1959b).

Nevertheless Doherty (personal communication, 1969) regrets that the work in North Queensland did not include a full double blind study which would have been generally acceptable.

As we have stressed repeatedly if leptospirosis is treated early enough with adequate doses of penicillin parenterally then the penicillin-leptospiral response is perhaps the quickest diagnostic test of all in the special circumstances of these cases (Mackay-Dick and Robinson 1957; Mackay-Dick and Robinson 1959a and 1959b). This particular point emphasises that blood for culture must be taken before the first dose of penicillin is given as a definite diagnosis may depend essentially on a positive blood culture in view of the fact that in cases treated in the early days of the illness antibodies may not be detectable in the ensuing weeks and so the agglutination reaction and other serological tests may be negative.

DISCUSSION.

The jungles of Eastern and Western Malaysia are leptospiral environments par excellence; and soldiers serving there who suffer from an abrupt influenza-like febrile illness with chills, headache, muscle pains and muscle tenderness, conjunctival suffusion and gastrointestinal symptoms with albumin and cellular elements in the urine should be diagnosed as leptospirosis until proved otherwise. However, a normal urine does not exclude leptospirosis.

Albuminuria may be present in 80 per cent of cases within 24 hours of admission to hospital, and when it is the sole abnormal urinary finding, as it may be in 47 per cent or so of cases it must not be dismissed as 'febrile albuminuria.' This point has been previously stressed (Mackay-Dick and Watts 1949; Mackay-Dick and Robinson 1957; Turner 1969).

Trimble (1956) in his series of 236 cases (Table 10) reports neck stiffness in 30 per cent, Kernig's sign in 10 per cent, abnormal cerebrospinal fluid in 3 per cent. This latter finding should guard against unnecessary lumbar puncture due to misleading clinical signs of meningitis the result of muscle tenderness. Trimble (1956) also found icterus in only 10 per cent of his series. It is suggested that the true overall incidence of icterus may even be less than 10 per cent as mild anicteric cases of leptospirosis are easy to miss.

Laboratory diagnosis is by blood culture and serological tests. The former may be negative if penicillin is given before blood samples

ANALYSIS OF SYMPTOMS IN 236 CASES OF LEPTOSPIROSIS PROVED BY AGGLUTINATION
AND/OR CULTURE ON FLETCHER'S MEDIUM (after Trimble).

	%		%		%
Headache ..	98	Sore throat ..	25	Tender below L. costal margin ..	5
Conjunctival injection ..	80	Glandular enlargement ..	25	Abnormal C.S.F. found ..	3
Renal involvement ..	70	Rigors ..	18	No conjunctival injection or pain or tenderness in body or limbs ..	3
(requiring gastric drip or I.V. glucose) ..	7	Bleeding ..	18	Total white count (extremes 4,000 to 30,000) averaged ..	9,000
Vomiting ..	60	Rash present ..	16	Polymorphonuclear percentage (extremes 20% to 96%) averaged ..	75
Back and body pains ..	60	Spleen palpable ..	15		
Limb pains ..	60	Liver palpable ..	15		
Muscle tenderness ..	50	Lumbar puncture performed ..	11		
Injected throat ..	45	Kernig's sign positive ..	10		
Abdominal pain ..	35	Icterus ..	10		
Neck stiffness ..	30	Tender below R. costal margin ..	10		
Cough ..	30				
Physical signs in lungs ..	25				

TABLE 10

are taken or from contaminants. In cases treated early in the septicaemic phase of the disease peak titres may be low (Mackay-Dick and Robinson 1957) and in some cases antibodies may not be demonstrable in the ensuing weeks (Gsell 1966).

Crystalline penicillin parenterally in doses of 600,000 units 4 hourly for the first 24 hours, and then 6 hourly to complete seven days, begun on or before day 5 of the onset is of undoubted therapeutic value: and in this stage of the disease it is normally accompanied by a characteristic Herxheimer-like reaction, 4-6 hours after the first 4 hourly dose of penicillin; but the reaction may occur in 50 per cent of cases when treatment is begun on day 6 or later.

This reaction, considered to be of such diagnostic significance as to merit the designation of diagnostic penicillin-leptospiroal response (PLR), may cause alarm to the physician and nursing staff, but any tendency to treat it with vasoconstrictors in any shape or form, e.g. nor-adrenaline intravenous drip, is to be avoided as such measures may be lethal. Masterly inactivity is the key to its management; and it is not to be confused with hypersensitivity reactions to penicillin per se, which on close scrutiny it does not resemble. It has been suggested that its severity, but not its diagnostic significance, may be lessened by intravenous hydrocortisone during the first 24 hours of penicillin therapy. This may be of special value in debilitated subjects.

It may be of significance that true secondary fever, not to

be confused with a secondary rise in temperature and often regarded as an immunity reaction or as a relapse, does not occur in cases of leptospirosis treated with adequate doses of penicillin over a period of seven days irrespective of the day of the illness that it is begun; and late complications e.g. iritis, do not occur.

Of 90 cases provisionally diagnosed as leptospirosis 84, (93 per cent), were proved in the laboratory but we remain convinced that the remainder were cases of leptospirosis in view of the pattern of response to penicillin therapy (Mackay-Dick and Robinson 1957). In all in Malaya we treated a total of 140 laboratory proved cases of leptospirosis (Mackay-Dick and Robinson 1959a) and there were no fatal cases and the pattern of response to penicillin therapy was consistent and repeated in our cases from Sabah and Sarawak during the Indonesian Confrontation.

In the therapy of the illness we stress that immediate attention should be given to the degree of water and electrolyte depletion, their remedy and the maintenance of proper hydration and electrolyte balance. We treated anuria with the Bull regime (Mackay-Dick and Robinson 1957) but such cases from Sabah and Sarawak during the confrontation with Indonesia were evacuated by air to a renal dialysis unit in Singapore. Prednisone has been recommended in complicated cases.

Water has been repeatedly incriminated as a vector of leptospirosis in man. Ideally the soldier should avoid all infected water, infected soil and contact with carriers of this disease but

that is not practicable on patrols in the jungle. When Commanders know that as many as 35 per cent of fevers in security forces from the jungles may be due to leptospirosis (McCrumb et al., 1957) and that this disease may affect so many members of a patrol as to make necessary its withdrawal from an important operation, they realise that leptospirosis is not only of military significance but a disease in which they must be well versed regarding its cause, prevention and evasive action to it. They know that where possible water for all purposes should be sterilised; the routes and sources of infection; the value of collecting rain water; that flood waters are foci of high infectiousness; when pools may be safe for recreational bathing; all things edible regarded as waste to be burned and buried in deep pits; if contact with infected water is obligatory during operations then as little contact as possible should be made and then not with the bare skin. They realise the special hazard of leptospirosis in the circumstances of river crossing, river in spate, dropped weapon(s) and repeated diving to retrieve same. In such cases of special exposure with almost inevitable high incidence of leptospirosis they ask for oral penicillin as a chemoprophylactic. They wonder why we have not yet produced a vaccine to combat this disease in Malaysia. These military commanders know that pathogenic leptospirae occur in the rivers, streams, shore sand and swamps in the Malaysian jungles and of the generalised leptospiral contamination of the Malaysian rainforest and they know how to keep the upper hand on this ever present enemy. They know that rats are

attracted by anything edible and that includes toilet soap which must not be left lying about; and that if food is to be kept free from the urine of rats and other carriers, it is to be kept in secure meat safes off the ground and with an impermeable roof. Also that mosquito nets do not just keep off mosquitoes and other nuisances but prevent rats from crawling over the sleeping soldier whom they may bite and urinate on at the same time.

In our series of cases (Mackay-Dick and Robinson 1957) we decided not to have a controlled trial for various reasons, namely, the striking response to our chemotherapeutic regimen in our first dozen cases; diagnosis is normally in retrospect and as there are at least 30 known serotypes in Malaysia we could not balance serotype for serotype except in retrospect: the identification of serotypes was time consuming and took place in London: blood cultures were frequently contaminated and so useless: our cases were drawn from the same leptospiral environments as those reported on by our predecessors and so we regarded their cases, and how they treated them as phantom controls (Mackay-Dick and Robinson 1959a). However, from 1956 onwards medical officers in Malaya (Cook 1959) and in Singapore (O'Brien 1966 - personal communication) and in Sabah and Sarawak during the Indonesian Confrontation (1963-66) confirm the pattern of response of cases of leptospirosis treated early with adequate doses of penicillin on the lines of Mackay-Dick and Robinson (1957).

Nevertheless it must be admitted that one doctor steadfastly

refused to treat leptospirosis with penicillin. He said that the penicillin-leptospiral response was potentially dangerous to his patients, that it caused anuria and precipitated haemorrhages and jaundice which might otherwise not have occurred. Our answer to that was 140 laboratory proved penicillin treated cases with no fatalities, no cases of secondary fever or of late complications e.g. iritis irrespective of whether penicillin was given early or late and when adequate penicillin was given on or before day 5 the patient was afebrile, happy and comfortable at the end of the penicillin-leptospiral response. Finally, it is not always possible to decide which cases that appear mild at first will become gravely ill if specific treatment is withheld (Mackay-Dick and Robinson 1959a). Eighty five per cent of our cases were mild to moderate and 15 per cent severe. Our experiences with leptospirosis in Sabah and Sarawak (Eastern Malaysia) during the Indonesian Confrontation were a repeat of those in Malaya (now Western Malaysia) during the emergency there, but we became more conscious of mass infections with leptospirosis and preventive measures.

CONCLUSIONS.

In leptospirosis, in which the natural history is initially a septicaemia, and where an appropriate bactericidal drug is available, the advantages of early diagnosis and prompt institution of an adequate drug regimen are self evident. To this end a knowledge of leptospiral environments, of the protean manifestations of this disease and of the territorial/occupational/residential history of the patient, as well as particular care to establish the day of the illness, are of special significance.

Crystalline penicillin parenterally in adequate dosage and frequency over a period of seven days prevents secondary fever and late complications: and if given in the septicaemic phase of this disease, particularly early, not only is it of definite therapeutic value in arresting the disease, but it is accompanied in 4-6 hours after the institution of 4 hourly parenteral penicillin by a Herxheimer-like reaction so characteristic to merit, it is suggested, the designation of the diagnostic penicillin-leptospiral response.

With such early exhibition of parenteral penicillin, antibodies may be well below diagnostic level or not even detectable in the ensuing weeks. Therefore in cases where blood culture is contaminated or where penicillin has been given before blood samples have been taken a diagnosis may have to be made on clinical grounds alone supported by the penicillin-leptospiral response in most cases where treatment has been begun on or before day 5 of the illness;

but this Herxheimer-like reaction may occur in cases treated later.

Prednisone may be of value in complicated cases as a cover for the first 24 hours of penicillin therapy to lessen the severity of the penicillin-leptospirosis response without diluting its diagnostic significance.

Otherwise treatment is to include water and electrolyte balance, optimum position of the patient during the hypotensive phase of the penicillin-leptospirosis response and the avoidance of vasoconstrictors which have proven lethal.

Significant preventive measures may be drawn up in view of our knowledge of leptospiral environments, sources of infection, modes of transmission and the role of water (and contaminated soil) as a vector in this disease; with special reference to the varying degrees of water infectivity which is at its maximum in flood waters in the rivers and streams in the Malaysian jungles and may be at its minimum, or possibly non-existent in the large pool, unprotected from the tropical sun and when not fed from flood waters such as the Bau Lake.

When bathing is to be permitted, for reasons of morale, it is important that it should not be permitted in a pool (or lake) within 24 hours of flood waters having flown in to it and that contact with the bank should be prevented by some form of platform and the bather not to have bare feet or to sit on the ground.

In cases of special exposure to leptospirosis on active service, when infection may render an important patrol non-effective,

the question of chemoprophylaxis e.g. oral penicillin is most significant; even more so is the provision of a multivalent vaccine containing the fewest possible serotypes and having a broad antigenic spectrum.

Experiences in Western Malaysia and Eastern Malaysia have reinforced the experience of the French in French Indo China that leptospirosis is a hazard of military significance.

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CANICOLA FEVER IN GERMANY

REPORT OF SIX CASES

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We report here six cases of canicola fever diagnosed in a British military hospital in Germany in the past few months. Only one other case has been notified previously from German sources in Germany, but it seems reasonable to assume that canicola fever is less rare in Germany than was formerly supposed, that its apparent rarity may be due to failure to diagnose cases as they arise, and that in the past this disease was diagnosed variously as jaundice, pneumonia, nephritis, infective gastritis or gastro-enteritis, benign meningitis, or influenza. Such diagnoses are apt to be made with great readiness, especially when cases do not receive the full investigations that they merit and when diagnoses are made on clinical grounds alone.

Vague diagnoses, such as primary atypical pneumonia, in the absence of cold agglutinins in the blood, may hide cases of canicola fever, Q fever, influenza, pneumo-typhoid, typhus fever, &c. Another vague diagnosis, benign lymphocytic meningitis, may be used in cases of canicola fever, infectious mononucleosis, non-paralytic anterior poliomyelitis, influenza, relapsing fever, meningo-typhoid, &c. Further, meningitis may be present without Kernig's sign, head-retraction, or neck-rigidity. We feel that cases of pyrexia of unknown origin, with headache, vomiting, and neck-stiffness, however slight, and even without Kernig's sign, should have a lumbar puncture done.

In cases of fever of dubious origin, albuminuria should not necessarily be regarded as being febrile in origin and dismissed as of little significance. Such cases merit a blood-urea estimation and repeated agglutination tests for leptospirosis. In all cases of "nephritis" a possible cause should be exhaustively and persistently sought. Febrile cases with nausea and vomiting may be diagnosed as gastritis, gastro-enteritis, or gastric influenza. In cases of undetermined origin a history of association with dogs should be sought and canicola

fever excluded. Canicola fever is a relatively benign disease—recovery is the rule—and so it is easy to see how diagnoses of benign meningitis, nephritis, atypical pneumonia, jaundice, &c., would pass unchallenged.

CASE-RECORDS

Case 1.—A young man, aged 19, was admitted to hospital with five days' history of general malaise, headache, vomiting, abdominal pain, and constipation. It was learnt later that he had bathed in the same semi-stagnant pool as case 2 about two weeks before the onset of symptoms. Past medical and family histories contained no relevant details.

On admission the only abnormal findings were a temperature of 102°F and albuminuria. His pulse-rate was 70 per min. There was a slight polymorph leucocytosis. A centrifuged deposit of the urine contained a few erythrocytes and leucocytes but no casts and was sterile on culture.

The patient's condition remained unchanged until the 9th day of the disease, when neck-stiffness and Kernig's sign were detected. The conjunctivæ were injected. There was no significant alteration in the leucocyte-count. Radiography of the chest revealed no abnormality. The cerebrospinal fluid (c.s.f.) contained 169 cells per ml. (polymorphs 20%, lymphocytes 80%). The protein content of the c.s.f. was 100 mg. per 100 ml. without excess of globulin. On the 12th day the c.s.f. contained 70 cells per c.mm. (polymorphs 12%, lymphocytes 88%) and 35 mg. of protein per 100 ml. On the same day the serum-bilirubin was 0.2 mg. per 100 ml. The blood-urea was 20 mg. per 100 ml. on the 10th day of the illness. Blood-serum collected on the 7th and 13th days of the illness contained significant and rising titres of antibodies to *Leptospira canicola*.

The patient's further progress was uneventful, and he was discharged from hospital on the 26th day of the disease having had symptomatic treatment only.

Case 2.—A man, aged 22, was admitted to hospital on the 9th day of an illness which had begun acutely with headache, vomiting, and diarrhoea, six watery stools being passed in two hours. General malaise, listlessness, excessive perspiration, anorexia, abdominal soreness, and several small epistaxes were noted in the subsequent 8 days. The patient was unfit for duty on the 3rd, 6th, and 7th days of the illness. He had a violent headache on the evening of the 8th day, and was referred to hospital. He described the headache as a continuous dull pain felt chiefly behind the eyes. It was worst in the mornings and was aggravated by coughing, sneezing, and hanging the head down. Severe bouts of headache were associated with vomiting.

The patient had bathed in the same semi-stagnant pool as case 1 about a fortnight before the onset of symptoms. He had had an uncomplicated attack of gonorrhoea in 1946. His past medical and family histories contained no other significant details.

On admission his temperature was 100°F, and pulse-rate 100 per min. Both conjunctivæ were grossly injected, with

subconjunctival ecchymoses. The optic discs were hyperæmic. A fine horizontal nystagmus was present on deviation of the eyes to the right. There was a non-paralytic internal strabismus of the right eye, but the patient said he had had a squint since childhood. There were no signs of meningeal irritation. No further abnormal physical signs developed.

The headache began to subside on the 11th day of the disease. Intermittent fever persisted until the 12th day, but all abnormal symptoms and signs disappeared by the 13th day.

A lumbar puncture on the 11th day of the illness produced clear fluid under a pressure of 120 mm.; there was no evidence of subarachnoid block. The C.S.F. contained 120 cells per ml. (polymorphs 20%, lymphocytes 80%); protein 70 mg. and chloride 760 mg. per 100 ml. Globulin was not present in excess. The white blood-cell count on the 10th day was 9400 per c.mm. (polymorphs 62%, lymphocytes 32%, eosinophils 4%, basophils 1%, monocytes 1%), and on the 14th day 10,600 per c.mm. (polymorphs 65%, lymphocytes 32%, basophils 2%, monocytes 1%). The blood-urea was 30 mg. per 100 ml. on the 14th day. All attempts to demonstrate leptospiruria were unsuccessful. Blood-serum collected on the 14th and 15th days of the illness contained significant titres of agglutinins to *L. canicola*.

The man's convalescence was uneventful, and he was discharged from hospital on the 28th day of the illness, having had only symptomatic treatment. Blood-serum collected on the 21st day from the onset of illness agglutinated *L. canicola* to a titre of 1 in 1000 and showed partial agglutination with *L. icterohæmorrhagiae* to 1 in 30.

Case 3.—A man, aged 34, was admitted to hospital with four days' history of general malaise, headache, myalgia, "feverishness," and excessive nocturnal perspiration. He had been in bed since the 3rd day of the illness. An unproductive cough had developed on the day of admission to hospital. He had served in the middle and far eastern theatres of war and had had malaria in 1933. His past medical and family histories contained no other relevant details.

On admission the predominant symptom was a dull boring pain behind the eyes; this was aggravated by movement of the eyes and by exposure to light. Temperature 101.8°F, pulse-rate 120 per min. Gross conjunctival infection, albuminuria, and muscle tenderness were the only other abnormal physical signs. A polymorph leucocytosis was present in the peripheral blood. No malarial parasites were detected in thick and thin blood films. A radiogram of the chest was normal. Blood-serum collected on the day of admission did not contain a significant titre of antibodies to *L. canicola*.

Headache and myalgia were more severe on the 6th day of the illness, when fever and a polymorph leucocytosis were still present and the blood-urea was 100 mg. per 100 ml. No malarial parasites were found on repeated examination of thick and thin blood films. A centrifuged deposit of urine contained a few erythrocytes and leucocytes but no casts and was sterile on culture. No leptospiræ were detected in

fresh warm alkaline specimens of urine at any stage of this man's illness.

The patient's condition was unchanged on the 7th day. No pathogenic organisms were detected by repeated microscopy and culture of the faeces. Fluoroscopy showed normal diaphragmatic mobility. The maxillary sinuses were opaque to X rays, but no pus was found on antrotomy and lavage. The Widal reaction was negative. No significant titre of agglutinins to brucella was detected. The patient's serum agglutinated *Proteus* OX2 at a dilution of 1 in 160, and OX19 at a dilution of 1 in 20, on the 9th day.

Retro-orbital pain, conjunctival injection, and muscle tenderness were worse on the 8th day. Slight resistance to flexion of the cervical spine was detected. Kernig's and Brudzinski's signs were negative. The optic discs were normal. The c.s.f. was under a pressure of 266 mm.; there was no evidence of subarachnoid block. The c.s.f. was opalescent and contained 446 leucocytes per ml. (polymorphs 67%, lymphocytes 33%); protein 80 mg. per 100 ml. with an excess of globulin; chloride 760 mg. per 100 ml.; Wassermann reaction negative. The serum-bilirubin was 0.2 mg. per 100 ml.

The patient was afebrile by the 10th day, and completely free from abnormal symptoms and signs by the 12th day. Blood-serum collected on the 11th and 21st days of the illness contained significant and rising titres of antibodies to *L. canicola*.

Convalescence was uneventful. A Paul-Bunnell reaction on the 23rd day was negative. A polymorph leucocytosis persisted in the peripheral blood after the clinical signs of infection had subsided. The cytology and chemistry of the c.s.f. had assumed their normal pattern, except for a slight excess of globulin, by the 27th day. The patient was discharged from hospital on the 35th day, having had only symptomatic treatment.

Case 4.—A man, aged 36, was admitted to hospital with four days' history of general malaise, anorexia, nausea, vomiting, and "feverishness." He had had malaria while a prisoner-of-war in the far east, but his past medical and family histories contained no other significant details. The patient's two dogs had had diarrhoea and appeared listless for several weeks before he was admitted to hospital. It was learnt subsequently that both animals had died about three weeks later, having had severe diarrhoea and loss of fur. Canine distemper had been diagnosed.

On admission the only abnormal findings were a temperature of 101°F, albuminuria, and a polymorph leucocytosis in the blood. No malarial parasites were detected in routine thick and thin blood films.

Conjunctival icterus, tenderness in the right hypochondrium, and bilirubinuria were present on the 6th day of the illness. Next day the patient's general condition was worse. He complained of general malaise and severe generalised headache. The jaundice was more intense, and he began to expectorate blood-streaked mucopurulent sputum. Fœtor oris was present. The optic discs were injected. The liver was

enlarged and tender, the lower border being palpable two finger-breadths below the right costal margin, and the liver dullness extending upwards to the level of the 7th rib in the right midaxillary line. Bilirubin and albumin were present in the urine, and a centrifuged deposit contained leucocytes and erythrocytes but no casts and was sterile on culture. No leptospiræ were detected in fresh warm alkalised urine at any stage of the illness. Blood-serum collected on the 7th day of the disease was later shown to contain a significant titre of agglutinins to *L. canicola*.

On the 8th day the patient complained of pain in his muscles and behind his eyes, the latter being aggravated by moving the eyes. The conjunctivæ were bright orange. The optic discs were more injected than before. Scattered râles were audible over both lung fields. A radiogram of the chest revealed scattered areas of consolidation in the right lung field, with a denser and more defined circular opacity about an inch in diameter in the subapical segment of the right upper lobe. Culture of the sputum yielded a mixed flora. The serum-bilirubin was 12 mg. per 100 ml. No malarial parasites were detected in thick and thin blood films collected at four-hour intervals over 24 hours. Penicillin was begun in a dosage of 50,000 units three-hourly.

The patient's condition was unchanged on the 9th day. A polymorph leucocytosis was still present in the blood. The blood-urea was 60 mg. per 100 ml. and the prothrombin-time was increased.

The patient's temperature was normal 48 hours after the start of penicillin therapy. On the 12th day of the illness he had been afebrile for 24 hours and was feeling better. The jaundice was less intense, and the pulmonary physical signs were less well marked. The lower border of the liver was palpable two finger-breadths below the right costal margin.

Penicillin was withheld on the 16th day of the illness after a total dosage of 2,300,000 units. The patient was then symptomless, and the blood-urea, serum-bilirubin, and leucocyte-count were within normal limits. A radiogram of the chest showed a well-defined right subapical opacity, which had been noted in the previous film, but no other abnormality. There were no abnormal pulmonary physical signs.

The following serological investigations were performed at this stage of the disease:

Estimation of titre of agglutinins to Herzerburg strain of <i>Rickettsia burneti</i>	Negative at 1 in 10.
Cold agglutination	Nil detected.
Complement-fixation test for antibody to psittacosis virus	Nil detected.
Paul-Bunnell reaction	Negative at 1 in 4.
Estimation of titre of anti-leptospiral agglutinins	Positive at 1 in 1000.
Hirst's test for antibodies to influenza viruses A and B	Negative.

Pyrexia recurred on the 17th day of the illness, the day after the cessation of penicillin therapy, and irregular fever persisted until the 42nd day, accompanied by profuse perspiration and a polymorph leucocytosis. A moderate general enlargement of lymph-glands was detected on the 22nd day.

There was no splenomegaly, and the hepatomegaly present earlier had now subsided.

No pathogenic organisms were detected by repeated microscopy and culture of the faeces. Diaphragmatic movements were normal. Blood-cultures were negative. Full examination of the upper respiratory tract, including radiological examination of the sinuses and antrum puncture, revealed no cause for the fever and leucocytosis. The Paul-Bunnell test remained negative. The Takata-Ara reaction was positive (+ +) and the serum-bilirubin was 0.2 mg. per 100 ml. on the 29th day.

Treatment with penicillin 60,000 units three-hourly was begun on the 29th day and continued until the 51st day.

The patient's condition improved slowly, and he left hospital about 60 days after the onset of the illness. There was no sequelæ. Convalescence was interrupted by bouts of severe sphenopalatine neuralgia, which was treated by anæsthetisation of the sphenopalatine ganglion on several occasions.

Case 5.—A woman, aged 26, became ill on Nov. 14, 1948, with an acute onset of general malaise, feverishness, anorexia, muscle pains, and retro-orbital headache. Next day she also complained of nausea, vomiting, and pains on moving the eyes. She was admitted to hospital on Nov. 19, the 6th day of pyrexia.

She had had no significant previous illnesses, except that in October, 1948, a week after being thoroughly soaked when out shooting, she had complained of urgency of micturition and noted that her urine was bloodstained. She was admitted to hospital next day and cystoscoped. With fluids ad lib and potassium citrate her urine became normal, and in about 5 days was discharged to full duty. She had had no urinary symptoms since. The hæmaturia was believed to have been due to oxaluria.

On admission her temperature was 101.2°F, pulse-rate 80, and respirations 20 per min.

On Nov. 20 the patient was febrile and complained of severe retro-orbital headache, pain in and around the eyes and on moving the eyes, muscle pains, and vomiting. There was no rash, no enlargement of the liver or spleen, no lymphadenopathy, and no conjunctival injection, although there was photophobia.

Radiography of the chest and sinuses showed nothing abnormal. Her white-cell count was 4300 per c.mm. (polymorphs 54%, lymphocytes 44%, monocytes 2%); Hb 95%. The urine was acid and contained albumin but no sugar; many epithelial cells and a few leucocytes were found microscopically. Cultures of blood and of urine were sterile.

On Nov. 21, the 8th day of pyrexia, her general condition remained unchanged, but there was definite though slight stiffness of the neck. Kernig's sign was not present.

Since the patient owned a lap-dog, we considered the neck stiffness to be an indication for lumbar puncture, but we did not do one, because there was a pustule on the skin.

Blood-serum taken on the 9th day of pyrexia showed partial agglutination to *L. icterohæmorrhagiae* and *L. canicola* in a dilution of 1 in 10. On the same day treatment was

started with intramuscular penicillin 200,000 units eight-hourly up to a total of 2,000,000 units.

Next day (Nov. 23) the patient's temperature was normal. She felt very much better, and there was no vomiting. She remained afebrile, her urine became normal, and she was discharged convalescent on Nov. 29.

The patient's blood and that of her dog were examined in December and found to be strongly positive for *L. canicola*; the findings were the same on Dec. 31 (47th day), when the patient had begun to complain again of pain in and behind her eyes just as she had during the febrile part of her illness.

On Feb. 5, 1949, she was readmitted to hospital with acute iritis which had started on Jan. 31 after she had watched a boxing tournament in a chilly and smoky atmosphere. Blood was taken for a leptospira-agglutination test on Feb. 8, the 86th day since the onset of the original illness, showed (see below). The Kahn flocculation test was negative. Investigations in this case are being continued.

Case 6.—A German maid, aged about 40, had a febrile illness similar to that of her mistress (case 5) but about a week later. On Feb. 8, 1949, about the 78th day from the onset of the illness, her blood was found to be positive for *L. canicola* to a titre of 1 in 300 and to agglutinate *L. icterohæmorrhagiae* to a titre of 1 in 10. On the same day blood from case 5 (86th day) was found to be positive for *L. canicola* to a titre of 1 in 300 and agglutinated *L. icterohæmorrhagiae* to 1 in 30. In view of the latest serological findings in case 5 "there seems no doubt that her maid was infected at the same time" (Dr. J. C. Broom, personal communication).

Case 5 said that both she and her maid wiped up her puppy's "pools" every day, so it is not unlikely that the disease was transmitted in each case through the skin of the hands which had come into contact with the infected puppy's urine.

The duration of the illness in case 6 was about the same as in case 5, but in case 6 the treatment was entirely symptomatic and there were no sequelæ or complications. No other investigations were carried out in case 6, who was treated at home under her own arrangements.

DISCUSSION

Canicola fever is by no means always mild. In case 4 the illness was very severe, suggesting infection with *L. icterohæmorrhagiae*.

Treatment in cases 1, 2, and 3 was entirely symptomatic. Case 5 seemed to respond rapidly to penicillin, but this may have been coincidental. In this case the recrudescence of pains in and behind the eyes, and on moving the eyes, at the end of December, 1948, is of interest, as is the onset of acute iritis on the 78th day. It might be useful to seek evidence of infection with *L. canicola* in all cases of apparently idiopathic acute iritis.

In case 4 intramuscular penicillin seems to have had a beneficial action both times it was used—30,000 units three-hourly for 9 days, and 60,000 units three-

hourly for 21 days. We feel that such cases with hepatic involvement and jaundice, with or without pulmonary infiltration, should be treated with large doses of penicillin for some weeks until the white-cell count is normal (if raised at the onset of treatment) and until all jaundice has gone and the lung fields are clear.

In cases 3 and 5 the lap-dogs gave positive serological tests for *L. canicola*, and case 4 had two dogs which both died from a vague illness which was characterised by diarrhoea and loss of fur and was diagnosed as severe distemper by a civilian veterinary surgeon. Patients with fever of uncertain origin should be closely questioned about ownership of, or association with, dogs. Case 4 admitted that his dogs often urinated on the vegetables in the kitchen, and that in his household vegetables were often served raw. Cases 1 and 2 had bathed in the same bathing-pool.

About eighty specimens of fresh warm alkaline urine collected at all stages of the disease in cases 1, 2, 3, and 4 were examined without success for *L. canicola*, and as a result we have given up this method of diagnostic investigation in such cases. Intraperitoneal injection of guineapigs proved unsuccessful. The golden hamster (*Cricetus auratus*) is the laboratory animal said to be the most susceptible to experimental infection with *L. canicola*. Agglutinin titres reached significant levels after the second week of the disease. Cross-agglutination with *L. icterohæmorrhagiae* may occur.

A polymorph leucocytosis was the usual hæmatological finding, but a normal total or differential leucocyte-count may be found in canicola fever. Atypical lymphocytes were present in the blood in case 4. So far as we are aware this finding has not been recorded previously in canicola fever.

Our recent experiences suggest that more general awareness of the manifestations of canicola fever and the more frequent use of serological reactions may reveal a higher incidence of this disease.

We wish to thank Major-General F. R. H. Mollan, O.B.E., M.C., D.M.S., British Army of the Rhine, for permission to publish this paper; Colonel J. B. George, commanding a British military hospital, B.A.O.R., for permission to forward this paper for publication and for help with case 5; Brigadier F. J. O'Meara, consulting physician, B.A.O.R., for his constant encouragement; the Wellcome Laboratories of Tropical Medicine for the serological investigations; Lieut.-Colonel R. L. Townsend, R.A.M.C., and Major H. J. Voss, R.A.M.C., for the other laboratory investigations and helpful advice; Captain W. T. Hendry, R.A.M.C., who was responsible for the management of case 1 and whose case notes we have used; and Lieutenant G. Freeman, R.A.M.C., otologist, for help with case 4.



PENICILLIN IN THE TREATMENT OF 84 CASES OF
LEPTOSPIROSIS IN MALAYA

BY

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LEPTOSPIROSIS is not a single entity but an infection caused by several different serotypes of leptospira (W.H.O., 1956), of which there are numerous varieties in Malaya.*

Conflicting opinions are held as to the therapeutic value of penicillin in leptospirosis. Highly optimistic views were expressed by Smith (1949) about the bactericidal and bacteriostatic action of penicillin on leptospiræ. He emphasised that penicillin should be administered within the first four days, during the septicæmic stage, and before toxic nephritis developed. Fairburn & Semple (1956), however, treated 21 cases of leptospirosis with 2,400,000 units of penicillin daily and concluded that penicillin was of no value in the treatment of this disease. Trimble (1957) appeared to hold similar views. Doherty (1955) studied 111 cases of early leptospirosis due to a variety of serotypes and found that the duration of the fever was significantly shorter in the 45 cases who had received more than 800,000 units of penicillin daily. Varfolomeeva (1951) treated 47 cases of leptospirosis without jaundice, the majority due to *Leptospira grippotyphosa*, with a total daily dose of 360,000 units of penicillin for four to five days and obtained a complete cure if treatment was begun before the fourth day of disease and modification of the illness when treatment was started between the fourth and seventh day. Referring to penicillin in leptospirosis, Broom (1953) noted that physicians very often recorded clinical improvement after its administration. Many individual cases and small series of the infection have been reported, and when the time of commencement of penicillin therapy and the dosage were comparable the results on the whole have corresponded with those of Doherty. Obviously, detailed knowledge of the natural course of the infection in humans due to each serotype would be of great value in assessing the efficacy of any therapeutic agent. What is of even greater importance in this assessment of the therapeutic value of penicillin in leptospirosis is the size

* *L. australis* A; *L. autumnalis*; *L. bangkinang*; *L. batavica*; *L. benjamin*; *L. canicola*; *L. celledoni*; *L. djasiman*; *L. grippotyphosa*; *L. hebdomadis*; *L. hyos*; *L. icterohæmorrhagica*; *L. javanica*; *L. ledanensis*; *L. poi*; *L. pomona*; *L. pyrogenes*; *L. saxkoebing*; *L. sentot*; *L. wolffii*.
m

and frequency of the dosage as well as the day on which such therapy was instituted. We suggest that the reason that some workers have reported disappointing results from penicillin therapy in leptospirosis is that insufficient importance has been attached to these points. In this communication we report on the diagnosis and treatment with penicillin of 84 cases of laboratory proven leptospirosis in Malaya.

MATERIALS AND METHODS

All cases were drawn from the security forces in Malaya and consisted of 41 United Kingdom troops and 43 Gurkhas. They had all been living in jungle camps or had been engaged on jungle patrols, and in fact 81 (96 per cent) of all cases first reported sick within ten days of returning from jungle patrol. The remaining three were living in jungle camps.

As far as possible, all male febrile cases admitted to B.M.H., Kinrara, were admitted to one ward. The medical officer in charge of that ward had been specially briefed in the diagnosis of leptospirosis and all febrile cases were seen by him as soon as possible after admission. The intention was that the provisional diagnosis of leptospirosis should be made, penicillin therapy instituted, and all relevant investigations begun within 24 hours of admission to hospital. This was achieved in 65 (77 per cent) of all laboratory proven cases of leptospirosis seen. Furthermore, out of 90 cases provisionally diagnosed and managed as leptospirosis, the laboratory subsequently confirmed the diagnosis in 84 cases.

All patients were sent to convalesce in the temperate climate of B.M.H., Cameron Highlands, at about the third to fourth week after the onset of their illness. On their return to B.M.H., Kinrara, they were reviewed and sent back to their units.

Cultural methods

Three tubes containing Fletcher's sterile rabbit serum on agar were used for each patient. One drop of blood was inoculated into each tube with sterile precautions. One tube was examined after 10 days' incubation and if no growth occurred the two remaining tubes were not examined until 28 days had elapsed. Because of the frequency of contamination an attempt was made to read the tubes before this became obvious.

Serological methods

Thirty millilitres of blood were taken initially. The serum was separated and stored in the cold, using one drop of 5 per cent sodium azide as a preservative. A second specimen was taken between the fifteenth and twentieth day of disease or immediately prior to discharge of the patient to convalescence. In positive cases a third specimen of serum was required late in convalescence to assist in the identification of the species of infecting leptospira. Such specimens normally had to be obtained direct from the regimental medical officer and were not requested as a routine.

A complement fixation test was performed at the United States Army Medical Research Unit, Kuala Lumpur, and was considered diagnostic of leptospirosis if the second specimen showed a fourfold rise in titre over the first. It cannot be regarded as specific, however, for the individual species of leptospira.

A leptospiral agglutination test was performed at the Wellcome Laboratories of Tropical Medicine, London. Although not usually regarded as species-specific on acute and early convalescent sera owing to the occurrence of cross-reactions, it often becomes specific when applied to late convalescent sera, on about the ninetieth day of the illness, by which time heterologous antibodies will usually have disappeared, leaving only homologous antibody.

According to Broom (personal communication) the agglutination technique used by the Wellcome Laboratories in diagnosing Malayan cases of leptospirosis is different from the ordinary diagnostic test for cases occurring in the United Kingdom, where only *L. icterohæmorrhagiæ* and *L. canicola* occur, because of the variety of species involved and the number of sera in which cross-reactions appear. Twenty serotypes are now tested by Broom, and the routine method used involves preliminary testing of the second sample of serum in a dilution of 1 in 100 against each of the twenty serotypes. If no agglutination occurs, the patient is considered as not suffering from leptospirosis. If the second sample gives a positive result with any of the antigens used, both first and second samples are tested against each of the serotypes with which the second reacts. If the first specimen is completely negative, or has a much lower titre than the second, a report "Positive for leptospirosis" is returned, provided that the second sample reacts to a dilution of at least 1 in 1,000 with one or more serotypes. If as sometimes happens both specimens are positive they usually react to about the same titre and with only one or two serotypes. Such cases are reported as positive, but it is suggested that the titres represent the residual antibodies from a previous infection and have no significance as far as the patient's present illness is concerned.

Routine investigations. Examinations of blood films for malaria were performed on all febrile cases and a specimen of urine was tested routinely. In addition, every patient had a total and differential white blood count performed and a radiograph of the chest taken. E.C.Gs. were done in selected cases (*vide infra*).

CLINICAL DIAGNOSIS

Symptoms

All cases complained of feverishness and 'flu'-like symptoms including headache, chills, generalised muscle pains, vomiting, cough, rigors and abdominal pain (see Table 1). Diarrhœa was a presenting symptom in four cases in the early stages of the disease and occurred in three cases within 24 hours of commencing treatment with penicillin. In one case diarrhœa began on the ninth day of the illness after five days of treatment. In all, 7 per cent of cases treated had severe diarrhœa, and in no case were pathogens discovered in the stools.

Signs

Conjunctival injection was present in 80 cases (95 per cent), muscle tenderness in 47 cases (56 per cent), generalised lymphadenopathy in 36 cases (43 per cent), tenderness in the upper right abdominal quadrant in 34 cases (40 per cent), adventitious signs in the chest in 23 cases (27 per cent), hepatomegaly in 15 cases (18 per cent), neck stiffness in 13 cases (15 per cent), splenomegaly in five cases (6 per cent) and herpes labialis in three cases (3.5 per cent). Towards the end of our series we noted œdema of the conjunctivæ in many patients, but as this sign had not been noticed before we were unable to assess its frequency throughout the series.

We would like to stress three points in the diagnosis of leptospirosis, in the absence of jaundice and hæmorrhage, shown by our series. None of our cases had the exquisite muscle tenderness reported by other observers; 95 per cent of our cases had obvious conjunctival injection, and rashes other than petechial hæmorrhages were not noted in a single case. On diagnosis, all cases felt and appeared ill and this was a striking feature when compared with other cases admitted to hospital with pyrexia of unknown origin.

Table 1. *Common symptoms in leptospirosis*

Day diagnosis was made	No. of cases	Fever	Head-ache	Chills	Rigors	Generalised muscle pains	Abdominal pain	Vomiting	Cough
2nd	4	4	4	2	2	3	2	2	1
3rd	15	15	15	12	2	9	0	6	2
4th	25	25	25	22	2	13	4	6	5
5th	26	26	26	22	4	16	4	12	10
6th	14	14	13	8	3	10	1	4	6
Total	84	84	83	66	13	51	11	30	24

COMPLICATIONS

Hæmorrhagic Phenomena

In 17 cases (20 per cent) hæmorrhages were present and in 10 of these they appeared shortly after penicillin therapy was commenced. In seven cases hæmoptysis occurred alone, in six hæmatemesis occurred alone, and in four hæmoptysis and hæmatemesis occurred together. In one case of hæmatemesis there were associated bleeding per rectum, epistaxis and petechial hæmorrhages into the skin. In one case of hæmoptysis there was associated epistaxis. In this series, hæmorrhages were not observed before the fourth day of the disease unless administration of penicillin had started.

Jaundice

Eighteen cases had jaundice. This appeared on the third day of the disease in two cases, on the fourth day in five cases, on the fifth day in seven cases and after the sixth day in four cases. It is interesting to note that jaundice became apparent shortly after the institution of penicillin therapy in several cases.

Five cases with icterus had associated hæmorrhages and these were seriously ill, the jaundice lasting 28 days. The remaining 13 cases ran a mild course and the average duration of icterus was seven days.

Urinary Changes

Of a total of 71 cases (84.5 per cent) which showed albuminuria or cylinduria while in hospital, 67 had urinary abnormalities on admission; 40 had albuminuria alone, whilst the remaining 27 showed cylinduria in addition. Four other cases developed albuminuria during their stay in hospital between the fifth and seventh day of illness.

There were five cases with anuria, which we defined as a condition when two ounces or less of urine are excreted in 24 hours. In two cases, admitted on the third and fourth day of the disease, anuria was present on admission. Of the remaining three cases, two were admitted on the fifth day and a third on the sixth day of the illness. All three became anuric following the commencement of penicillin therapy. The two cases admitted on the fifth day of the disease started penicillin within 24 and 48 hours of admission respectively, while the case admitted on the sixth day of the disease commenced penicillin three days after admission.

Four of the cases of anuria had associated jaundice and hæmorrhage. No case developed polyuria of low specific gravity following the anuric phase, as is frequently observed in cases of anuria following infections for which no specific cure is available, *e.g.* epidemic hæmorrhagic fever in Korea. It is noteworthy that all cases of anuria showed low systolic blood pressure, but no cardio-vascular stimulants were given as this might have precipitated sudden death.

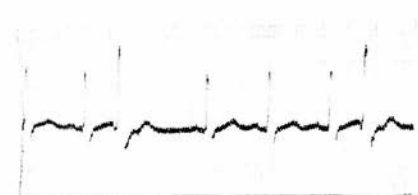
Radiography of the chest

In every case a radiograph of the chest was taken on admission, and further films were taken if hæmoptysis occurred or abnormal physical signs appeared in the chest. Thirteen per cent of all cases had abnormal chest radiographs of which three showed generally increased lung markings while eight showed bilateral mottling particularly at the bases. All cases in which mottling had been present during the acute stage had normal films after 10 days. In one case, showing mottled shadows, hæmoptysis was absent, while three cases with hæmoptysis had normal chest radiographs.

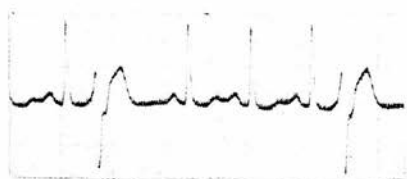
E.C.G. changes

The occurrence of myocarditis has been reported in leptospirosis (Dragert, 1934; Ashe, Pratt-Thomas & Kumpe, 1941; Sutliff, Shepard & Dunham, 1953), and for that reason, and because of past experience of collapse and death within hours in leptospirosis, we decided to obtain E.C.G. tracings in some cases. Bertucci (1945), referring only to Weil's disease due to *L. icterohæmorrhagiæ*, stated that the electrocardiogram occasionally showed prolonged QT and PR intervals, defective AV conduction, functional or real incomplete AV

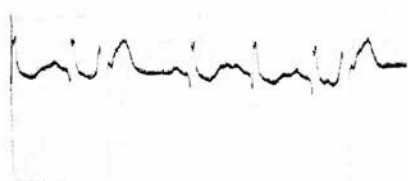
STANDARD E.C.G. LEADS OF CASE 1.



I

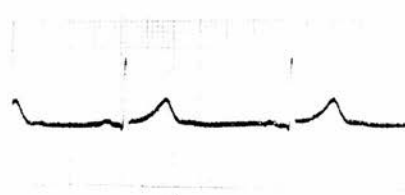


II

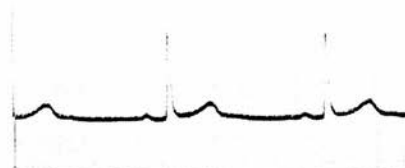


III

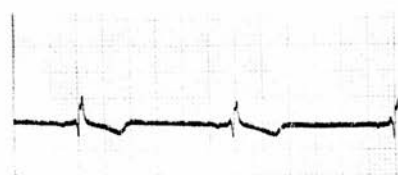
3rd day of disease showing ventricular extrasystoles tachycardia and low T waves in I and II, inverted T wave in III with a low voltage tracing.



I



II



III

12th day of disease showing almost complete reversion to normal tracing.

PLATE I

blocks, low T waves, blocked auricular beats, sinus tachycardia and low voltage QRS complexes, these changes being reversible during convalescence. Other workers report evidence of myocarditis on post-mortem examination.

Serial E.C.Gs. were performed on 10 of our cases. Four of these were selected on the grounds of clinical indications of myocardial disease, as shown by severe prolonged hypotension and irregularities of the pulse. The remaining six cases were consecutive admissions with uncomplicated leptospirosis of moderate severity. In all cases the first tracing was taken shortly after treatment with penicillin was started. A second tracing was taken during the stage of recovery, and in the case of abnormal results a third was obtained during convalescence.

The four patients with clinical signs of myocardial disease all showed E.C.G. evidence of myocarditis and are described below.

Case 1. Third day of disease. Gurkha soldier. Low voltage tracing with frequent ventricular extrasystoles and low T waves in leads I and II (see Plate I). By the twelfth day of disease the tracing had returned to normal.

Case 2. Fifth day of disease. Gurkha soldier. Low voltage tracing with widening of the QRS complex (0.14 secs.) and low T waves in lead II and all V leads. By the seventh day of disease the tracing showed the T waves to be approaching normality and by the fourteenth day of disease the E.C.G. was normal.

Case 3. Fifth day of disease. British soldier, aged 21. Low voltage tracing with low T waves in Leads I and II. Normal by the fourteenth day of disease.

Case 4. Fourth day of disease. Gurkha soldier showed auricular fibrillation together with widening of the QRS complex and depressed T waves in all leads. Fibrillation lasted for eight hours and the E.C.G. returned to normal by the tenth day of disease.

Of the six consecutive uncomplicated cases, two showed minor irregularities of the QRST complex on the fifth day of the disease, which returned to normal by the seventh day. The remaining four cases showed no E.C.G. changes other than sinus tachycardia.

Blood count

In all cases there was a relative or absolute polymorpho-nuclear leucocytosis with a total white cell count varying from 4,100/c.mm. to 20,300/c.mm. The average white cell count was between 8,000/c.mm. and 9,000/c.mm.

Cerebro-spinal fluid

Lumbar puncture was performed on three occasions and the cerebro-spinal fluids found to be normal.

Severity of cases

The illness was considered to be severe when serious complications such

as multiple hæmorrhages, severe myocarditis and severe jaundice or anuria occurred (see Table 2).

Table 2. *Cases classified according to severity*

Day of disease on which treatment started	Number of cases	Severity of illness	
		Mild	Severe
2nd	4	3	1
3rd	15	11	4
4th	25	22	3
5th	26	25	1
6th	14	10	4

RESULTS OF SPECIAL INVESTIGATIONS

Blood culture was positive in 29 per cent of cases, of which six were taken on the third day, eight on the fourth day, nine on the fifth day and one after the sixth day of the illness. We are unable to assess accurately the results of the complement fixation test (CFT) as towards the end of this series the antigen used gave inconsistent results.

In 39 per cent of cases the agglutination reaction (AGR) alone was positive, while in 25 per cent of cases the CFT and AGR were positive in the absence of a positive blood culture. In six cases the CFT was the only positive finding when the second specimen of serum for the AGR was damaged in transit. Only in one case was the CFT positive when both blood culture and AGR were negative. The presence of a positive CFT makes the diagnosis certain, but on occasion this test may be negative when other tests are positive (see Table 3).

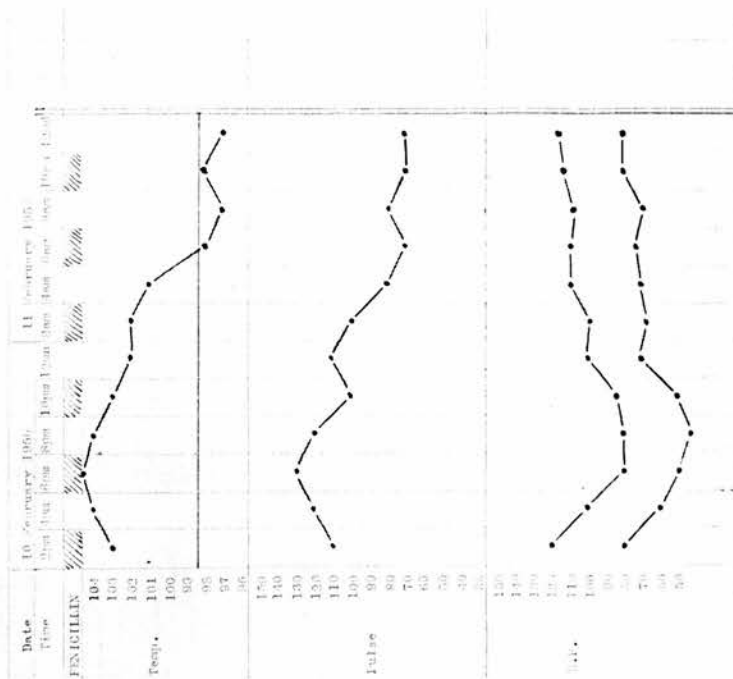
Table 3. *Results of blood culture, complement fixation test (CFT) and agglutination*

No of cases	Blood culture	CFT	AGR
12	Positive	Positive	Positive
6	Positive	Negative	Positive
5	Positive	Negative	Not done*
1	Positive	Positive	Not done*
32	Negative	Negative	Positive
21	Negative	Positive	Positive
6	Negative	Positive	Not done*
1	Negative	Positive	Negative

* The AGR was not performed in these cases as the bottle containing the second specimen was broken in transit.

It should be mentioned that in several cases where the blood culture was positive the AGR titre in the second specimen was not diagnostic. Broom agrees that these must be regarded as true cases of leptospirosis in which the production of antibodies is unusually slow, and possibly the earlier administration of penicillin may explain this phenomenon. Furthermore, one patient had a second attack of leptospirosis, due to a different species from the first, after

3rd DAY OF DISTANCE



Daily and 2-hourly charts showing response to Penicillin. Note the effect on the temperature, pulse rate and blood pressure.

PLATE II

an interval of months and both attacks responded dramatically to penicillin therapy.

In another case with a positive blood culture, serological tests showed that the culture reacted to titre with antisera from both *L. bataviae* and *L. medanensis*, both being unrelated antigenically. Broom is of the opinion that the possibility of a concurrent infection with the two serotypes cannot be excluded.

OUTLINE OF TREATMENT

The aim of treatment was to maintain adequate hydration and electrolyte balance, to relieve headache and pain with pethidine and to commence penicillin therapy as soon as possible.

It was calculated that obviously dehydrated patients required 6 per cent of their body-weight as fluid replacement. Half of this fluid was given by continuous intravenous drip as normal saline and half as 5 per cent dextrose in water in the absence of renal impairment. In the presence of vomiting, equivalent volume of normal saline was given by intravenous infusion. The average daily basic requirement was assessed as three litres of fluid in 24 hours, one-sixth of this was given as normal saline and five-sixths as 5 per cent dextrose in water. Where the patient had oliguria due to impaired renal function the régime was modified accordingly.

The initial dose of penicillin was 600,000 units given intramuscularly, and this dose was repeated four-hourly for 24 hours and then six-hourly until the seven days therapy had been completed.

All five cases of anuria were managed with a régime first described by Bull, Joecks & Lowe (1949) and did well. Three patients who developed anuria before this series was started would not tolerate this régime. In these, however, we restored a reasonable state of hydration and electrolyte balance intravenously. We gave two pints of 40 per cent glucose in water by continuous infusion through polythene tubing into the inferior vena cava. All three patients survived although two had been dangerously ill and had hæmorrhagic manifestations and deep jaundice.

EFFECTS OF PENICILLIN THERAPY

When penicillin was given before the sixth day of the illness the duration of the fever was reduced from an average of about 34 hours to one of about 18 hours. At the same time the symptoms were ameliorated (see Plate II).

When penicillin was given on or after the sixth day of the illness no reduction in the period of pyrexia was observed, although in individual cases the symptoms were relieved and the fever fell more rapidly than in untreated cases.

Clinical reactions to penicillin therapy

Within four to six hours of the first dose of intramuscular penicillin, 70 (83 per cent) of all cases and 89 per cent of those treated within five days of the onset of the illness had a reaction similar to that described by Jarisch and Herxheimer. Of these 70 cases, 59 had a sharp rise in temperature while 58

had a marked fall in blood pressure. In addition, in 31 cases there was a precipitation or aggravation of the classical symptoms and signs of leptospirosis. The reaction was mild in 60 and severe in 10 affected cases.

Some alarm was caused by the collapse and appearance of these patients, but penicillin therapy was continued and no additional treatment prescribed. Within 24 hours the patients had completely recovered from their reaction, the duration of which approximately equalled that of the pyrexia following the commencement of penicillin therapy.

This type of reaction has been noted elsewhere during penicillin therapy for leptospirosis (Crooks & Blair, 1955) so that we neither ceased nor modified the antibiotic therapy. We came to regard this reaction as an indication of a good response to treatment and as a useful diagnostic sign in leptospirosis. It is now known in this hospital as the "Diagnostic Penicillin-Leptospiral Response."

We noted that during the hours immediately following the onset of the reaction, a high specific gravity oliguria occurred in all cases except in the three who became anuric. Once the blood pressure returned to normal, the urinary output did likewise without the passage of persistently low specific gravity urine.

The average duration of hypotension was 24 hours, although in cases in which penicillin therapy was started after the fifth day of the illness, the blood pressure was rather low before treatment (averaging 110/70) and slowly returned to normal within seven days (see Tables 4 and 5).

Table 4. *Penicillin Leptospiral Response (P.L.R)*

Day of disease on which treatment was begun	Total No. of cases	No. of cases showing a P.L.R.	Percentage showing P.L.R.	Severity of P.L.R.	
				Mild	Severe
2nd	4	4	100	3	1
3rd	15	13	86	8	5
4th	25	22	88	19	3
5th	26	23	88	23	0
6th	14	8	57	7	1

Table 5. *Nature of P.L.R.*

No. of cases showing sharp rise in temperature	Average temperature	No. of cases showing fall of blood pressure	Lowest blood pressure recorded	No. of cases in which symptoms or signs were precipitated or aggravated by penicillin
3	105° F.	3	90/60 mm. of Hg.	3
11	105° F.	13	90/60 mm. of Hg.	10
16	104° F.	20	80/50 mm. of Hg.	8
22	104° F.	17	80/50 mm. of Hg.	4
7	103° F.	5	80/50 mm. of Hg.	6

An additional feature noted in our patients was the absence of prolonged impairment of the concentrating power of the kidney, which had been a frequent complication in the past in patients not receiving penicillin. In the experience of one of us (J. M-D) it was not an infrequent occurrence in cases of lepto-

spirosis not treated with penicillin for a relapse to occur during the third week of the illness, so that patients were never sent to convalesce before the end of the third week. Such relapses were characterised by a sudden steep rise of temperature, associated with rigors of varying degree and a recrudescence of some of the symptoms and signs of leptospirosis. Within 24 to 36 hours the temperature returned to normal and the patient again became symptom-free.

Our findings indicate that penicillin given within five days of the onset of leptospirosis has a definite therapeutic value. We also believe that penicillin should be given no matter on what day of the disease the patient comes under medical care. The dramatic response of the illness seen in patients treated earlier is absent in these late cases, but it is felt that relapse will be avoided. In addition, penicillin may also prevent any prolonged impairment of renal concentrating power.

DISCUSSION

In assessing the therapeutic value of a drug in a given infection, an understanding of the natural history of the disease produced by the infecting agent in humans is essential, together with a detailed knowledge of the early symptomatology and presenting signs.

Pathogenic leptospiræ are known to occur particularly in the mud and swamps of the Malayan jungles, so that the patient who had returned from jungle patrols and living in jungle camps was suspect, especially as malaria and typhus were improbable when the soldier had taken normal precautions.

We believe that the early clinical diagnosis of leptospirosis is not difficult, despite the fact that in this hospital, where there is an awareness of the problem and excellent hospital laboratory and local research facilities, 30 per cent of all febrile cases admitted do in fact suffer from a mild infection of as yet unknown ætiology.

The patient suffers from a sharp, febrile, 'flu'-like illness with obvious conjunctival injection, sometimes associated with œdema of the conjunctiva. In addition he may complain of vomiting and abdominal pains, as well as muscle pains and tenderness. On examination he may be jaundiced, with or without hepatomegaly, or show only some upper abdominal tenderness, general lymphadenopathy and vague signs in the chest. Relative or absolute polymorphonuclear leucocytosis is invariable, and malaria is excluded by repeated thick and thin blood smears.

Within 24 hours of admission to hospital, albuminuria is present in 80 per cent of cases, and in our experience a febrile patient from a leptospiral environment with suggestive symptoms and albuminuria should be diagnosed provisionally as suffering from leptospirosis and the urinary signs not dismissed as febrile albuminuria. This point has been previously stressed (Mackay-Dick & Watts, 1949).

The frequency of radiological signs in the chest was interesting to note, especially in the absence of hæmoptysis, but in all cases the signs disappeared after 10 days.

Of the 90 cases provisionally diagnosed as leptospirosis, 84 (93 per cent) were proved in the laboratory. Although we should be content with this high diagnostic rate, we noted that several of the six remaining cases showed a response following penicillin and we are not convinced that the provisional diagnosis was false even though the blood culture, CFT and AGR were all negative. As we have shown, the blood culture can be positive, and yet with early penicillin therapy the rise in antibody titre may be below the diagnostic level unless very late specimens are examined. As blood culture was negative in 71 per cent of cases it will be appreciated that a negative or doubtful positive AGR in the second specimen of serum in cases treated early with adequate doses of penicillin may not exclude a diagnosis of leptospirosis.

We were particularly interested in the therapy of the illness and stress that immediate attention should be given to the degree of water and electrolyte depletion, their remedy and the maintenance of proper hydration and electrolyte balance. In the presence of anuria the routine was to adopt the Bull régime, and this was satisfactory in our five cases presenting this complication. Should this not have proved satisfactory we had intended to give one litre of 40 per cent glucose into the inferior vena cava every 24 hours, which had proved life-saving in three previous cases (Russell, Dewhurst & Brace, 1954).

With skilled hydration and attention to the electrolyte balance alone, we believe that all but fulminating cases of leptospirosis should recover, provided that the significance of hypotension and myocarditis is recognised and no attempt is made to prescribe cardiac stimulants. Can we therefore claim that penicillin is of therapeutic value in the treatment of leptospirosis in Malaya? We have demonstrated that the duration of the fever is reduced to about half and that symptoms are relieved when this therapy is begun within the first five days of illness. In those cases treated after the first five days none showed any impairment of the water concentrating power of the kidney either early or late in the illness, and there were no relapses; nor did any of the remaining 70 cases show such features. This is in contrast to the experience of one of us (J.M-D.) when not using penicillin in the treatment of leptospirosis, when all febrile cases who developed persistent impairment of the water concentrating power of the kidney were suspected of having leptospirosis and relapses in the third week were not infrequent.

Past experience of hypotension in patients suffering from leptospirosis suggests that cardio-vascular stimulants have no place in the treatment of this complication. The presence of jaundice called for no additional special therapeutic measures in the early stages. Attention was paid to the accepted dietetic principles when the patient was out of danger.

SUMMARY

Details are given of the diagnosis, management and treatment of 84 consecutive cases of laboratory proven leptospirosis affecting security forces in Malaya. The presenting symptoms and signs of the cases are reviewed and the importance of albuminuria in the diagnosis stressed.

The incidence of radiological changes in the lungs is noted. Attention is drawn to the presence of myocarditis in some cases and the importance of avoiding treating this complication with cardio-vascular stimulants.

Leptospirosis should be managed by careful maintenance of the water and electrolyte balance, together with early treatment with large doses of penicillin. 600,000 units of crystalline penicillin were given four-hourly on the first day and the same dose six-hourly for a further six days. This halved the duration of the fever and cured symptoms rapidly when given in the first five days of the illness, prevented any relapse and eliminated the danger of persistent impairment of renal concentrating power in all cases.

We suggest that large doses of penicillin should be given in all cases of leptospirosis no matter how long the diagnosis is delayed.

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